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Editor
ROY WALDO MINER

BASIC ODOR RESEARCH CORRELATION

BY

ALBERT R. BEHNKE (*General Chairman*), THOMAS H. URDAHL (*Conference Chairman*), W. W. BATES, L. H. BECK, L. M. BEIDLER, P. CALABRESI, J. A. CAMPBELL, L. C. CARTWRIGHT, J. E. CHRISTIAN, F. R. DARKIS, N. DEININGER, V. G. DETHIER, H. W. DORN, J. R. EATON, A. G. EMSLIE, J. GREENSPAN, E. J. HACKNEY, R. M. HAINER, A. JACOBSON, P. H. KELLEY, E. J. KENNEY, L. KRUGER, R. L. KUEHNER, E. LAWSON, L. LEISERSON, J. H. MASSERMAN, J. F. MATESON, R. W. MONCRIEFF, M. M. MOZELL, C. PECHTEL, C. PFAFFMAN, K. H. PRIBRAM, E. REED, W. E. REYNOLDS, C. ROYS, C. R. SPEALMAN, F. SULLIVAN, J. B. SUMNER, A. TURK, AND B. M. WENZEL.

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ROY WALDO MINER

BASIC ODOR RESEARCH CORRELATION*

General Chairman: ALBERT R. BEHNKE
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*This series of papers is the result of a Conference on *Basic Odor Research Correlation* held by the New York Academy of Sciences in cooperation with The American Society of Heating and Ventilating Engineers, April 23 and 24, 1953.

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Part I. The Odor Problem in Industry and Sciences

BASIC ODOR RESEARCH CORRELATION: INTRODUCTION

By Albert R. Behnke
Captain (MC), U. S. Navy

As an introduction to this monograph on Basic Odor Research Correlation, I shall take the liberty of projecting our vision to the year 1983, rather than to discuss directly our problems as in the present year of 1953.

The scene, therefore, is in a hypothetical Presidium of Science of that time, and it is our pleasure to review the three decades of progress in our knowledge of the olfactory sense.

Let us especially recall a scientific meeting held in 1953. At that time, the American Society of Heating and Ventilating Engineers reaffirmed its faith in the experimental method and, under the auspices of the famous old New York Academy of Sciences, gathered a group of distinguished investigators and industrial authorities to promote basic odor research correlation.

Then, the everyday problem was to eliminate or suppress unpleasant but harmless odors and to develop hedonic substitutes. The meeting was concerned primarily with the basic investigations that had rendered the applied endeavor meaningful.

What was the status of problems and research relative to odor in 1953? In comparison with vision and hearing, quantitative knowledge referable to taste and smell was limited. Thus, in Steven's *Handbook of Experimental Psychology* (now out of print), 25 pages were devoted to taste and smell (10 pages to smell, alone), 128 pages to hearing, and 171 to vision.

Individuals who do little or no investigative work tend to dwell on the general lack of interest in olfactory problems, on misconceptions, on poor instrumentation, and even question the quality of research. Perspective, however, permits a better evaluation. The olfactory sense, being an alarm system or a probing device, has a phenomenal sensitivity but an indifferent intensity discrimination ($\Delta I/I$). Moreover, the olfactory sense needs to operate only transiently. These three characteristics posed difficulties to the osmologist, for they required that he measure extremely low concentrations very rapidly, and they precluded differential characterization. In contrast to stimuli of vision and audition, which were characterized simply by frequency and amplitude, those of olfaction involved, essentially, the specification of chemical reactivity.

In both auditory and visual systems, it had proved possible to correlate definite anatomical structures with definite specialties of the function; *e.g.*, position in the cochlea with pitch, rods in the retina with night vision, *etc.* Secondly, the retinogram had been definitely correlated with psychophysical effects in the same subject. Finally, *in vitro* systems, reconstituted from retinal extracts, had been shown to duplicate essential features of the visual function. At midcentury, osmics boasted none of these achievements. In the olfactory system, many receptive messages in response to odorant stimuli appeared to be concentrated in a few transferring pathways whose projections in the nervous system represented a diffuse miscellany, as compared, for instance, with the orderly spatial arrangement of the cochlear mechanism and its projection at various levels in the central nervous system.

Already in 1953, however, certain essential features of the olfactory process pointed unequivocally to its underlying nature. Having brushed aside the archaic distinction between "chemical" and "physical" processes, we were confronted with the thermodynamic fact that the reaction of the odorant with the mucosa could not *directly* provide the energy for exciting the nervous endings, since the energy thus generated was too small by at least one order of magnitude. In the parlance of the day, the receptor had to be equipped with a chemical amplifier, or "enzyme," controlling, as it were, a great flux of energy and rendering the whole stream vulnerable to tiny amounts of those substances to which it was subject (The semantics of the decade delayed the recognition that no fundamental difference existed between the enzyme hypothesis and the permeability hypothesis, since both were only pictorial versions of the chemical amplifier).

A second roadmark was the obvious diversity of odorants that excite the mucosa. This feature could only mean that *the molecule with which the odorant reacted* (what we know today as *olfactase*) was a molecule of considerable complexity, capable of undergoing reaction with many totally different odorants. Some of our contemporary chemists, who laid great stress on the quantitative relationships between odorants of the same homologous series, were disturbed by the fact that molecules of diverse structure and reactivity could also be odorants belonging to the same qualitative group. We must, of course, not be unduly harsh since, in those days, the astonishing polyfunctionality and adaptability of *G*-proteins had only been established for serum albumin and globulin. Nevertheless, it is true that this feature of diversity clearly pointed to a macromolecule, if not a protein, as the target substance of the odorant.

Although, in the early days of olfactory research, physiologists and psychologists were prone to regard "masking" and "adaptation" as forbidding obstacles to any sensible theory, it was rapidly recognized by some that the phenomenon known to early biochemists as "competitive interaction" might readily account for masking. Adaptation proved in the end a harder nut to crack. Part of the difficulty arose because, for some time, investigators preferred to gloss over the problem in vague terms. Even in 1953, any searching analyst would have concluded that the enzyme hypothesis, in its contemporary form, could not account for adaptation. Also, prior to the era of chemoelectric preparations, it was impossible to foretell that adaptation had its origin partly in the receptor, where the odorant-olfactase complex was rapidly reversed by odorant antibodies; and partly in the brain, where the "differentiating circuits" of the old-fashioned cyberneticists saw to it that only rapidly *varying* signals reached the conscious level.

It was from considerations such as these that a North American chemist deduced the essentials of the olfactase system by sheer logic, far in advance of any confirmatory evidence. Putting Kistiakowsky's quaint old phraseology in present-day terms, we may recount his suggestion* that the fundamental olfactory "organ" might be a system of catalyzed reactions in the stationary state, supplying a constant flux of power to the depolarizing oscillators of the primary neurones. Kistiakowsky pictured the odorants as enzyme inhibitors (several years later

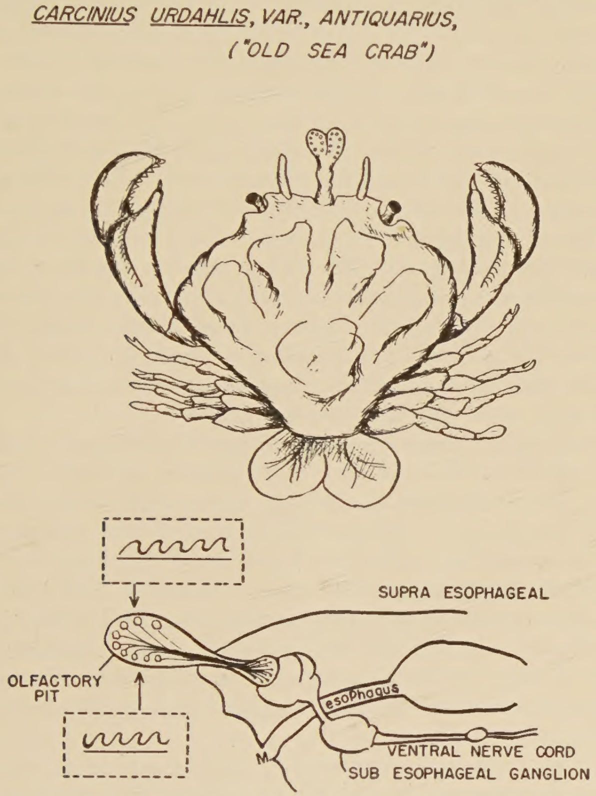

Figure 1. *Carcinius urdahlis* var. *antiquarius* (Old Sea Crab). The bilobed olfactory end organ, with nine receptors reacting specifically to nine groups of primary odorants. The lower diagram shows the sinusoidal wave recorded from a single primary unit responding to odorants having the surrealist configuration. The supra esophageal ganglion, the sub esophageal ganglion, the ventral nerve cord, and the esophagus are also shown.

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* Doctor Jerome Alexander's pioneer considerations in this field are gratefully acknowledged.

it was recognized that some odorants were activating rather than inhibiting agents, and this led to the modern term *modifiers*) able to affect the neuronal discharge by governing the characteristics of the energy supply.

The real experimental advances in olfaction, however, only became possible after the major zoological discovery of 1962. The old reactor submarine *Nautilus*, operated by the Pan-American Science Clubs, ran upon and caught unharmed several specimens of *Carcinius urdahlis* var. *antiquarius*, *coll.*, Old Sea Crab (FIGURE 1). This interesting creature was found to possess unusually long and lightly protected stretches of chemosensory nerve, subject to easy piercing by internal glass electrodes. Moreover, the inverted giant-celled mucosa was easily accessible to the type of cytological observation that Le Gros Clark conducted with much more difficult specimens some 40 years ago. It was unfortunate that Professor Adrian did not begin his pioneer work with this species.

In a brief span of five years the quantitative relation was elucidated between afferent neuronal discharge, *i.e.*, the electro-olfactogram (E.O.G.), and controlled stimuli. This line of research enjoyed still greater impetus by the application of radioactive odorants whose quantity could be readily metered, and whose microlocation could be unequivocally established by scintillation counters. The spectacular data attending the use of intravenous radioisotopes of substances giving rise to the sensation of odor need not be reviewed here.

The exploitation of these methods progressively confirmed the hypothesis that odorants affected enzymes, which, in turn, controlled an energy flux. The variations in the flux were, as we have said, detected indirectly by the E.O.G. Meanwhile, renewed midcentury interest in microcalorimetry had led to the development of ultrasensitive collimating detectors and, by these means, the energy flux was ultimately measured *in situ* and related both to odorant binding and the E.O.G.

Thus, in the late sixties, practically every indirect means of deducing the operation of enzymes in the mucosa of *C. urdahlis* had been exhausted, and intensive biochemical work to isolate and purify the responsible substances began in earnest.

Actually, olfactase was successfully extracted at a comparatively early stage in the research, but it went unrecognized because, in isolated form, it did not manifest the properties characteristic of its operation *in situ*. Thus, once again we learned the painful lesson that some physiological properties could be reconstructed *in vitro* only by properly organized systems of enzymes. Following these early failures, however, progress once again accelerated. The purification and crystallization of *G*-olfactase by the Scandinavians, just less than ten rotations ago, was a modern tribute to the tedious but rewarding methods established by Doctor James B. Sumner early in this century. We are all familiar with the brilliant sequence that followed. Under the sponsorship of a special commission of the Presidium, and with the almost lavish support of our industrial colleagues, laboratories all over the planet showed that the olfactases properly adsorbed on syntex could be coupled with the enzymes of the metabolic pool, and that the entire system injected into test cells would cause repetitive depolarization of the cell surface whose frequency was delicately altered in the presence of odorants. This magnificent chapter was, so to speak, the grand finale on the fundamental study of olfaction, but parallel to this development there have been three decades of progress in applied osmics, whose importance to high standards of habitability can scarcely be overestimated.

By midcentury, for example, the measurement of olfactory performance among large populations was still in its infancy and, still hampered by the persistent use of large, untrained populations rather than the small well-characterized and highly trained populations employed in our modern olfactoria. Systematic testing of such groups in theatres, public conveyances, and naval vessels (especially submarines) had scarcely begun. It remained for the future to assess the sources of discomfort and to devise rational methods for their elimination. By 1960, however, following the synthesis of the first odorant-specific adsorbents, and the development of new and powerful statistical techniques, olfactory testing became a true science. Technical developments in auxiliary sciences, of course, underlay all pure research in osmics, but they also contributed immensely to technology. Even before the work on olfactase, the growing knowledge of molecular structure and molecular interactions guided empirical work in classifying odorants. We have already mentioned the analytic value of molecularly-shaped specific adsorbents, such as syntex. To these should be added the microspectrometers, capable of covering the electromagnetic spectrum from far infrared to far ultraviolet, the emission electron microscope, and the analytical mass spectrometer. The forerunners of all these devices existed in 1953, but osmologists of that day were a little slow in realizing their potentialities. The uncovering and exploring of certain fascinating natural history problems were incidental to osmic research. The effect of experimentally-induced anosmias in species peculiarly dependent on the olfactory sense has been studied exhaustively and profitably, but in Southern America and in Southern Asia. A great deal of our modern knowledge on the physiology and biochemistry of symbiosis originated in the clinical investigations of air exhausted from the cages of the odorless germ-free animals, first prepared around midcentury by Reyniers in North America. Concomitantly, medical and welfare scientists, aided by extensive analyses of air surrounding and exchanging with individual persons, developed the present-day concept of the molecular aura of the human body, and its variations in health and disease. Finally, the otherwise deplorable war tensions did serve to stimulate interest in sharpening the individual olfactory sense, and in improving judgment of olfactory sensations. Thus, eventually, the sense of smell reassumed its evolutionary role as a first-line alarm system, ranking in this respect with or above vision and audition.

Certain sidelights of olfactory research are also of sociological interest. For example, in the sphere of politics, the replacement of animal symbols by emblems of fragrant flowers (*e.g.* the donkey and the elephant by the rose and the gardenia) is due, unquestionably, to extensive advertising campaigns. Olfactory research illustrated the value of organized and unified information. At the 1953 meeting of the old New York Academy of Sciences, the American Society of Heating and Ventilating Engineers (forerunners of our Comfort Corps) agreed to compile a glossary of technical terms pertaining to the psychophysics and general characteristics of olfaction, which has since become standard. Another accomplishment was a research analysis of the chief current endeavors pertaining to olfaction with a detailed and cross-indexed description of the progress and background of all basic investigations. This analysis included, further, a list of names of investigators, laboratories, the equipment on hand, the funds spent, as well as estimates of future work contemplated with a notation of funds and equipment required. Finally, it was in osmics that commercial firms took the lead, not only in converting spaces filled with smoke and otherwise malodorous air into chambers of invigorating fragrance, but also in establishing a most generous fellowship and grant program designed to accelerate the then lagging pace of osmic research.

Addendum (*historical item*). "In the course of exploration of the frontal lobe of a psychotic patient, the tip of the recording depth electrode was placed in the vicinity of the olfactory bulb. It was subsequently shown that a rhythmic response to a stimulus of smell similar to that obtained by Adrian could be recorded from the depth electrode. This response is of considerable interest, not only because it is the first recording of waves related to olfaction in man, but also because it is the first instance in man in which a continuous stimulus has been shown to give rise to a rhythmic potential discharge.

"The measurements of the frequencies associated with the various odors showed a considerable scatter during the tests of any particular substance and a very marked overlap when the whole group is considered. Therefore, it seems unlikely that the frequency of response is an important factor in discrimination of smell unless the brain possesses an extremely sensitive frequency-analyzing system. With regard to discrimination of intensity, the evidence indicates that there is a definite and possibly almost linear relationship between intensity of stimulus and response. This would seem to suggest that the message transferring information concerning the intensity of smell takes the form of an amplitude-modulation rather than a frequency-modulation system which has been found to underlie most afferent transmitting systems." "Human Olfactory Responses Recorded by Depth Electrography," Proc. Staff Meetings, Mayo Clinic. **28** (6), 1953.

Acknowledgment

I am indebted to many friends, whose ready wit and scorn for conventional facts inspired what color may exist in these pages. On the serious side, Professor Frank A. Geldard made available to me material from his recently published book on the human senses, and Doctor Henry Imus and Doctor William Berry of the Office of Naval Research brought to my attention an outstanding review and critique prepared by Doctors F. Nowell and Margaret H. Jones.

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THE PROBLEM OF ODOR IN THE CIGARETTE INDUSTRY

By F. R. Darkis, E. J. Hackney, W. W. Bates, and Lee Leiserson
The Liggett and Myers Tobacco Company, Durham, N. C.

Introduction

Tobacco and tobacco products are very adsorbent and will become impregnated with the odors from most odoriferous substances with which they come in contact. The presence on the tobacco of very small amounts of either added or adsorbed odoriferous materials in most instances brings about significant changes in the flavor and taste of the smoke, which are out of all proportion to the amount of such materials present. The flavor and taste of cigarette smoke are important factors in making cigarettes desired by the public.

Once foreign odors impregnate tobaccos, it is extremely difficult to remove those odors (by processes presently available) without seriously damaging the flavor and taste factors of the smoke obtained from these tobaccos. Undesirable foreign odors often may be masked by the use of added aromatics. Even if one is skilled in the art of treating tobaccos with flavors, however, he may use materials that are not compatible with either the natural odors of the tobacco or the foreign odor or perhaps both. If such be the case, the smoke from the resultant mixture will lack the flavor of smoke produced by natural well-aged tobaccos which seems to be attractive to the consumer, and he will criticize the product and may discontinue its use.

The only safe procedure with tobacco and tobacco products is to protect them from the presence of materials that may impart foreign odors, and treat them in such a manner that the loss of natural odors is minimized. The substances which impart the attractive, satiating, and pleasure-producing properties to the flavor and aroma of cigarette smoke are primarily those which are innate to the tissue of the tobacco leaf. Therefore, it is advantageous that the new or unaged leaf be treated under such conditions that the maximum of desirable properties is developed during the process of aging and manufacturing, and concomitantly, that the tobacco be protected from odors not natural to the aged leaf, and that basic changes in the leaf tissue which may produce irritating substances and those which impart off flavors to the smoke be minimized.

At present, the most practical approach to the determination of the odor properties of tobaccos and tobacco smoke is the organoleptic one. The consumer has used this method of evaluating tobacco products over the centuries. Formal panels, however, organized and trained to study the taste, flavor, and aroma properties of tobaccos and tobacco smoke have been in existence only during recent years. The organoleptic technique, as applied to cigarette smoke, has been improved, and a high degree of confidence is being placed in organoleptic findings relative to cigarette smoking.

The odor problem may be divided into three distinct categories as follows:

(1) Foreign odors that may contaminate the tobacco before the manufacturer received it.

(2) The development, retention, and protection of the natural odor of the tobacco while undergoing aging and processing.

(3) The creating, stabilizing, and maintaining of the desired level and character of the aromatic properties of the cigarette from the stage of blending the tobacco to the time of the consumption of the cigarette.

The Source and Effect of Off Odors that Develop in Tobacco before It Is Purchased by the Manufacturer

The manufacturer has but little control over the growing and curing of tobacco other than the selection of the tobaccos which he purchases. Tobacco, while in the hands of some growers, may be exposed to one or more of three main sources of odor contamination: (1) odors from the residues of organic insecticides applied to the plant while in the field; (2) odors developed and adsorbed during the curing process; and (3) odors adsorbed from foreign materials and those developed as a result of the action of micro-organisms on the tobacco during storage on the farms.

The newer organic insecticides that have been applied to tobacco plants for the control of leaf-eating insects include Benzene Hexachloride, Aldrin, Dieldrin, Toxaphene, Parathion, and Rothane. The first three of these, if present on the tobacco tissue even in concentrations of less than 100 parts per million, will cause the smoke to impart a sharp, burning sensation to the membranes of the mouth and nose. At these concentrations, it is difficult to detect the presence of these materials by the sense of smell. Toxaphene, if present in less than 100 parts per million, is difficult to detect. The smoke from the tobacco containing it, however, is astringent to the lips and imparts a burning sensation to the membranes of the nose. Rothane in concentrations of less than 100 parts per million seems not to impart objectionable properties to the smoke. If organic insecticides are present on the leaf in large concentrations, the buyer can detect their odor and refuse to buy the tobacco. When present in low concentrations, they may not be detected by the buyer, resulting in a loss to the manufacturer if detected later; or, if they get into the product going to the consumer, they may cause a decrease in consumer satisfaction.

Some growers use either poorly designed or defective oil burning equipment in curing bright tobacco. Tobacco so cured usually possesses off odors which resemble those of petroleum products. These tobaccos can usually be detected and avoided by the buyers. Some growers, in curing either bright or air-cured tobaccos, use coal or coke which is high in sulfur content. This material may impart a very characteristic acrid odor to the tobacco. This tobacco can usually be avoided because of odor and physical appearance.

The cured tobaccos may be stored on the farm for periods of a few days to several months before they are placed on the market. During this period of storage on some farms they are exposed to odors from animals, fowls, manures, fertilizers, petroleum products, *etc*. Depending upon the level, these odors may or may not impart objectionable features to the smoke of the aged tobacco. On some farms storage facilities are not sufficient to protect the tobacco from decay due to mold. If the tobacco molds, it may be possible either to remove the odor of the mold by the application of heat, or hide it by the use of additives. If the grower should resort to the latter practice, it may be difficult to detect the fact that the tobacco had molded before it got into the cigarette. The presence in a cigarette of tobacco that has molded at any time in its existence can be detected by organoleptic means by a trained panel, and it is likely to be detected by the discriminating smoker.

The Development and the Retention of Aroma in Tobacco during Aging and Processing

The moisture content of the tobacco when the manufacturer buys it from the grower varies over a wide range. The manufacturer reduces the moisture content below that which is desirable for aging and then brings it up to the desired moisture content. This process, known as re-drying, needs to be carried out under conditions which remove moisture from the tobacco without unduly increasing the temperature of the tobacco tissue. An increase in the vapor pressure of the aromatic constituents resulting in a diminution of their content is not desirable. The removal of irritants by the principle of steam or vapor distillation, however, is advantageous.

After re-drying, the tobacco is kept in storage for an average period of two years. Aging is necessary to develop the high level of pleasing aroma which is associated with the better quality, well-aged tobaccos. As tobacco is very hygroscopic, it is packaged in large compact masses and storage facilities are provided to protect it from rapid changes in humidity. If this is not done, the tobacco will increase in moisture content, and during periods of warm weather will decay due to mold growth. Molded tobacco is a loss as it is not suitable for manufacture of cigarettes. The odor due to the growth of mold is extremely difficult to remove. If it is covered up by additives, it can still be perceived in the taste of the smoke. In addition to protecting the stored tobacco from atmospheric moisture and mold, the manufacturer needs to strive to store the tobacco at a moisture content high enough to promote active and optimum aging. The margin of safety separating the two processes is quite narrow. If the moisture content of the stored tobacco is less than 10 per cent, the aroma development is very slow; and if it is above 13 per cent, the possibility of mold development is very real.

In addition to the actual losses of tobacco in storage caused by the tobacco beetle and the tobacco moth (the most destructive insects found in stored tobaccos), the musty earthy odor resulting from the action of these insects is very objectionable, therefore tobaccos should be protected from these insects. Fumigation of tobaccos is effective but usually impracticable. Treatment of the storage areas with the newer organic insecticides is fairly effective and practicable; but if these materials come in contact with the tobacco, their presence is likely to impart undesirable flavor characteristics to the smoke. The use of pyrethrin sprays or fogs in the storage areas is fairly effective but expensive.

In the manufacturing processes great care must be exercised to remove any foreign material of the nature of cotton, wool, rubber, asphalt, feathers, resinous wood, *etc.*, which are used in handling the tobacco on the farm or which may come in contact with it before the manufacturer receives it. In the factory it is necessary to take strict precautions at all stages to be sure that similar materials which are used in the construction of the various conveyor systems and in the clothing of the personnel do not find their way into the tobacco. The presence of these substances does not affect the odor of the tobacco; however, they have a very detrimental effect upon the odor and flavor of the smoke produced by the tobacco.

Recently the installation of air conditioning systems in the manufacturing areas of the cigarette factories has posed serious problems that were not originally anticipated. The aged tobacco, as it is undergoing the various heat and moisture treatments before it is incorporated into the cigarette, liberates a pleasant-smelling aroma. The volatile substances which give rise to this aroma seem to change rapidly in the presence of the air and give rise to volatiles which impart a somewhat flat, stale, and pungent sensation to the nose. In the conventional air conditioning system these volatiles are recirculated and are readsorbed by the tobacco, thereby imparting less pleasant aromatic properties to the smoke of the cigarette.

In the design of air conditioning systems for tobacco factories, it is very important to use as much fresh air as possible and as little re-circulated air as possible, and to scrub thoroughly all air before introducing it into the manufacturing spaces. The scrubber removes minute pieces of tobacco from the re-circulated air. These provide an excellent medium for the action of micro-organisms. The scrubbing water needs to be chemically treated and the system frequently cleaned so as to prevent their action and thus protect the tobacco from another source of undesirable odors.

The materials given off from tobacco are acid in nature. They seem not to react with stainless steel and to react slowly with galvanized iron. However, they tend to corode aluminum and copper very rapidly.

The Production, Stabilizing, and Protection of the Aroma of the Product that the Consumer Uses

The manufacturer is faced with the problem of offering the consuming public a brand name product that is constant in respect to the aroma of the cigarette and the flavor and aroma of the cigarette smoke. Due primarily to changing climatic conditions, the aromatic properties of tobaccos vary from season to season and from area to area in the tobacco-producing belts. This makes it necessary for the manufacturer to have a large stock of tobaccos from a wide cross section of the tobacco-producing areas if he is to be able to produce continuously a blend of tobacco whose aromatic properties are either constant or change at such a slow rate that they are not detected by the consumer.

Each successful manufacturer has developed a blend of tobaccos which he believes has distinctive aroma and other characterizing properties and which produces a smoke that is pleasing to a large segment of the public. If he depends upon the natural properties of the blend to furnish these characteristics, he needs to guard against all odors which are foreign to tobacco. One of the sources of these odors is cosmetics. Tobacco will absorb the odor from most cosmetics. As these have a high level of fragrance, they are readily perceptible by the consumer.

Some manufacturers apply aromatic additives to the blend of tobaccos. These are used primarily as an aid in covering up variations in the aroma of the natural tobaccos, and to standardize and characterize the aroma of the package of cigarettes. In some instances these additives are carried along with the smoke stream into the mouth. The principal flavors and aroma which the consumer appreciates after he has lighted the cigarette are furnished by tobacco and not by the additives. If the latter fail to enhance the pleasure of the act of smoking the cigarette, their use is of questionable value.

The flavoring of tobaccos is still an art. The experienced and ingenious flavoring experts have considerable difficulty in compounding satisfactory aromatic flavors for tobacco products. It is necessary that they be compatible with the true aroma of the blend, cover up unwanted odors, and smooth out the flavor of the smoke without introducing harsh and peculiar effects which are not attractive to the consumer. In compounding the finished cigarette, it is necessary to consider the compatibility of the blend of tobaccos not only with the added odorants but to consider the combination of these with all materials other than tobacco which may be used in fabricating and packaging the cigarette. For example, the various resins and plasticizers used in the fabrication of filter tips, cork tips, and wrappers, and the various adhesives used in constructing and packaging the cigarette may have an effect upon its final aromatic properties.

Cigarettes are normally packaged in several layers of material. It is usually assumed that the only purpose of these materials is that of protecting the cigarette from changes in its moisture content. These wrappings, however, preserve the aromatic properties of the cigarette and protect it from the adsorption of foreign odors. Cigarettes require protection from odors associated with petroleum products, foods and spices, cosmetics and perfumes, disinfectants, other tobacco products, and odors associated with the atmosphere of congested areas.

THE PROBLEMS OF CONTROLLING ODORS IN PROCESSING PROTEIN FOODS

By Herman W. Dorn
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Introduction

Invariably, a food or drug industry will locate its plants on the outskirts of a community where the problem of odor will not constitute a major issue until such outlying areas become heavily inhabited. It is certain, therefore, that the management of such industries has definitely anticipated conditions wherein objectionable odors may result from known and unknown processes. Temporary advantages may be thus secured by such suburban locations which minimize odor complaints because of the very few persons affected in any sparsely settled area and the few structures to hamper the rapid atmospheric dispersion of materials disturbing to the olfactory senses. Indeed, few or no complaints would be entered by employees and, certainly, less by employers even though they may dwell in the more immediate vicinity of an offensive odor source.

The following types of protein food plants were visited and studied with regard to determining the nature of the process odors and possible methods for correcting them: Fish canneries; factories manufacturing soy, corn, and wheat products; sugar beet refineries; sugar beet waste products and rendering works, as well as slaughter houses. In all of these industries, there existed, concurrently with the vapor odor problems, the exigencies of liquid wastes and their related challenges of corrosion and irrecoverable product losses. Additionally, there was present the possibility of toxicity due to chemical or biological concentrations having been brought up to undesirable levels even in the presence of attempts to confine such liquids within the limits of comparatively closed systems such as pipes, kettles, or tanks.

In the final analysis, it was observed that the odors connected with the liquid wastes were far more difficult to subdue or eliminate than the vapor odors arising from the various processing stages and operations of the particular industries concerned. Most commonly, the odor-producing vapor problems were more satisfactorily handled apart from the odor-producing liquids. In each case, however, a central collection chamber was customarily established for the material in question prior to treatment.

Liquid Waste Odors

In all of the protein food plants surveyed, greatest concern was expressed regarding the control of odor problems associated with the liquid wastes. Because of this, it is of interest to consider some of these factors first. It would appear that the food manufacturer initially attempts to solve his major odor and waste disposal difficulties by discharging the troublesome fluid into any neighboring sewer, stream, or river available. Under such conditions, if there are no subsequent "cease and desist" orders from the authorities, the problem no longer exists. If, however, the community's sewage system suddenly manifests signs of marked corrosion and leakage, or if marine life and shore vegetation begin to exhibit signs of devastation, considerable revision is indicated in the local industrial effluent program.

A somewhat tardy, but careful analysis of the waste now reveals, in addition to pungency, a liquid either very acidic or very high in biochemical oxygen demand, and sometimes both. Some wastes were observed to have a pH of 2 or less as well as a B.O.D. of 150,000! Frequently, it was possible to pool the waste temporarily in a sump pit where it was neutralized with calcium carbonate or lime wastes from the beet sugar process. The B.O.D. was often decreased by the addition of measured quantities of commercial hydrogen peroxide. After considerable agitation, followed by filtration, such a treated effluent was found more acceptable to community disposal systems and water outlets.

Many plants, prior to resorting to treatment of wastes, particularly where no outlet was available, turned to apparently less expensive methods for handling the liquids. Some of these procedures were very crude indeed and involved the use of storage pits, vented tanks, waste dumps dependent upon slow ground seepage for drainage flow, and pools covering several acres in certain cases. The severe limitations of any and all forms of such storage activities became rapidly and conclusively evident to all concerned. It was not surprising to observe such errors in fundamental judgment by an industry in distress because usually the greater the pressure that existed for solving these situations, the more arbitrary and less technically correct was the managerial answer, particularly in the sugar beet industry. These temporary expedients ultimately resulted in complex projects of land clearance, chemical treatment, and conduit construction.

One plant with a severe odor-waste problem and with no current sewerage facilities, but well equipped with multiple-effect evaporators, concluded that it would be more economical to concentrate its wastes and then combust them in a Nichols-Herreshoff-type roaster or furnace, rather than use extensive sewer tiles and pretreatment to permit tying the commercial sewer line into the neighboring community system.

Where some form of waste outlet was available, the following liquid operations have provided a marked degree of satisfactory pretreatment to eliminate the more objectionable odors of the industries previously mentioned:

(1) Chemical neutralization followed by filtration;

(2) Oxidation by use of peroxide;

(3) Use of excess chlorine or chlorine compounds followed by the addition of sulfur dioxide. This method usually converts many of the offensive to inoffensive compounds, but also converts the excess chlorine to the corrosive hydrochloric acid;

(4) Neutralization by ion exchange which also adsorbs many of the odor constituents;

(5) Treatment with activated carbons of the Nuchar and Darco types, followed by an agitation period and filtration.

Depending upon the particular industrial waste concerned, combinations of the above-mentioned methods have yielded reasonably successful results. The holding period necessary for treating the liquids cuts down the disposal rate sufficiently to require large volume tanks and filter operations which must run after the plant has stopped or decreased its daily production. The activated carbon method was found effective in removing odor-producing animal and vegetable oils from the wastes whereas the ion exchange resins were without effect in this regard. When considerable quantities of oil were found present in the effluents, a coarser mesh carbon (No. 40-60) was most desirable, since it did not hamper filtration rates seriously, yet provided sufficient active adsorption surface to remain economically feasible. This was particularly true of wastes from fish canneries, rendering plants, and soy bean processing units where the beans had been previously oil-extracted by expression rather than by solvent methods.

When liquid waste products from vegetable protein sources were studied for odor-producing components, not only were the nitrogenous and sulfur-containing substances responsible for offense, but also the lower homologue dibasic and monobasic acids. The fish and animal tankage were additionally complicated by putrefying protein products, although trimethyl amine, primary, and secondary amines were found in both fish and sugar beet residues. These substances, together with rancid oils, made up the general odor problems although, through chemical process degradation, some aldehydes and ketones were detected.

Filter cakes from odor-removal processes constituted a serious problem if stored for any period of time. The retained material underwent degradation and the heat of reaction was sufficient, under certain conditions, to bring about spontaneous combustion and a consequent release of odors far more irritating than those present in the original waste liquids. The most successful method for disposing of the filter cake proved to be a Nichols-Herreshoff type roaster. The combustion process was so rapid and effective that the volatile odor constituents were destroyed before they could escape to the surrounding atmosphere.

Vapor Waste Odors

The problems attendant upon odors arising from industrial process liquids are, therefore, more specifically related to the work of the sanitary engineer. The problems of odors produced by manufacturing process vapors, however, are more akin to the corrective methods practiced by the ventilating engineer. The difficult structural factors, which are present in setting up a central vapor collection chamber to which are connected the numerous exhaust ducts throughout any given chemical plant, are primarily due to corrosion and frequently inconvenient occupation of overhead space. The duct system must be amply provided with condensation traps even when the structural material consists of Transite.

A simple odor adsorption tower utilized by some smaller food plants makes use of a structure of chemical-ware fitted with baffle shelves and loosely packed with a very coarse glass fiber. The vapors are conducted counter-currently and upward against a fine spray of water from a nozzle system.

When the vapors were strongly acidic and the odor components less readily picked up by the water spray, a current of ammonia gas introduced with the chemical vapors usually proved fairly successful in diminishing the escape of odor. One plant utilized a dry process tower, bringing together the odor vapors and anhydrous ammonia, then releasing the mixture as a finely dispersed "dust" over the surrounding countryside. Over a period of months, a number of phenomenal events were observed to occur. Certain barren patches of waste land began to sprout vegetation, homes several thousand feet away acquired a faint but persistent odor, window glass in the neighborhood remained cloudy despite continual washing, and green lawns took on a white-wash appearance. The dry disposal method was soon modified by popular demand.

Where odor problems were fairly localized within a given building, counter-odors frequently were employed. These agents are of particular interest because they possess a greater rate of solubility on the nasal membranes than the offensive odor, and so compete in the activation of the olfactory senses. Considerable caution is required in selecting counter-odors because the odor combinations that may result with the improper agent usually are more offensive than the original odor to be eliminated. Currently, there are also on the market types of counter-odors which have mild anesthetizing properties. Except in limited and confined conditions, such odor agents have little industrial value despite the extensive use of atomizing sprays and ingenious dispersion methods available.

One of the most interesting studies on the chemical degradation of odor compounds has been performed with ozone. Although this powerful oxidizing agent can be formed in many ways, its commercial manufacture has been only by the electrostatic method, the production yield being approximately proportional to the electrostatic intensity, and to the frequency in the case of alternating current. The better ozone generators have smooth electrodes and dielectrics and are built in either the plate or cylindrical form. Their voltage operation ranges from 5000 to 25,000, and the frequency range is 50 to 500 cycles. Actually, the cylindrical ozonizers are more compact and more economical to operate than the plate form. Some commercial units yield 60g/kw-hr at a concentration of 2 to 3 grams per cubic meter of air.

The Siemens' ozonizer consists of two concentric tubes with the inner tube metal-coated on its inner surface, whereas the Berthelot or Brodie ozone tube replaces the metallic coating with sulfuric acid. The oxygen used in the apparatus must be dried in order to obtain maximum yields of ozone.

By introducing a stream of ozonated oxygen into a central collection chamber of odor-producing vapors, a definite release of inoffensive vapor was readily accomplished. The costs, however, were very nearly prohibitive. The units utilizing the ozonizing of air were much more reasonable yet only partially as effective since the ozone concentration in ozonized *oxygen* can be readily maintained for prolonged periods at 0.1 per cent by volume, which is about 500 times greater than the ozonized *air* producer.

The use of adsorption agents in tower systems netted the most successful results in the removal of odors from process vapors. A study of silica gel, because of its ease of regeneration and convenience, revealed it to be too readily exhausted by water vapor even though its carbon compound vapor uptake was fair for short periods of time.

When ion exchange earths and resins were used for odor removal, special tower packing was required to maintain the moisture content of the exchanger materials since they became totally ineffective on evaporation due to the rapid passage of air over them. Also, the exchangers were not sufficiently rapid in adsorptive capacity to effect efficient odor removal for commercial requirements. More studies on the synthetic exchange resins may provide an interesting aspect of the odor removal research now in progress.

Without question, the most satisfactory method for eliminating odors from air was found in the use of activated carbon. The specific carbon, however, for the specific job it must perform is the prime factor in its selection. Chars made from different woods vary widely among themselves, and commercial carbons for vapor adsorption vary widely in porosity, density, hardness, and wetting properties. Generally, the adsorption of the vapors is inversely proportional to their molecular volumes and the temperature, but directly proportional to the pressure. It is apparent, too, that an excess of moisture in the odor-ladened vapors will rapidly decrease the adsorption capacity of the carbon by destroying the maximum effective adsorption surface available. To overcome this problem, the vapors are passed over a cooling coil and the condensate run off with the effluent. This technique also diminishes the formation of hot spots in the relatively thick, activated carbon bed. As the vapor is taken up at the gas-entrance of the bed, the carbon reaches its saturation point before the vapor reaches the exit end of the chamber. Of course, as the process continues, more of the carbon is used up, but there is a variable degree of vapor saturation between the entrance and exit.

As odor vapors are adsorbed by the carbon, heat is liberated; and if this heat is not removed, the carbon bed functions with decreasing efficiency. The previously-mentioned cooling coil system is thus shown to have multiple advantages since the increased life of the active carbon ultimately pays for the cooling arrangement. The adsorbed vapors retained by the carbon at normal temperatures can be readily released when low-pressure steam is introduced. Many firms prefer to burn the used carbon, however, rather than chance releasing the odors again. Good commercial practice has shown that the carbon bed should be constructed with section shelves capable of ready replacement to maintain over-all adsorption efficiency.

The carbon beds are preferably made up of Columbia Carbon granular particles (4 to 8 mesh) through which the gas from which the vapor is to be adsorbed can be passed. These larger sizes of carbon are necessary in order to keep the gas flow resistance to a minimum. In recent years, extruded and preformed blocks and rods of activated carbon have been prepared for several special gas adsorption uses. A modification of these carbon forms is the multiple canister filter tower for odor removal using a tilted shelf arrangement. Each canister is 4 inches in diameter by 11 inches tall, and contains a cylindrical layer of 6 to 14 mesh carbon about ¾ inch thick. These canisters are rated at 25 cu. ft. per min. of air at a pressure drop of about ⅛ inch of water. The carbon can be reactivated by high temperature treatment, although many who use them refill the units with a new charge of material rather than try to work over the exhausted carbon.

The vapor odor problems are still not satisfactorily handled even though these procedures have all received some favor in the numerous food industries. Our methods to date are but approximations of the over-all answers because we do not fully comprehend the nature of those compounds which give rise to odors and because of the variability of the conditions encountered in each plant.

Some Legal Aspects

When authoritative pressure is brought to bear upon the solution of a given commercial odor problem, it is done first by complaint, then by injunction causing the entire operation to stop until satisfactory assurance is given that the odor will not reoccur. There is some leniency of the law when it is proved that the odor is not a toxic vapor. When the odor, however, is sufficiently objectionable purely from a psychological standpoint, the question of local property values will then enter the discussion and usually will effect a legal decision against the plant concerned.

The detrimental effects of an effluent upon neighboring rivers, vegetation, and marine life have already been discussed as has been the damage to community sewage systems. It is therefore possible to visualize entire plants at a standstill for lack of technical skill and imagination in handling what may initially be considered an odor problem of minor significance. This paper remains as testimony that such has needlessly been the case in several unfortunate instances.

Summary

A number of methods have been described which were utilized in controlling odors arising from the liquid and vapor phases of processing protein food products within, and neighboring, the corporate limits of a well-inhabited community. The following liquid operations provided some degree of satisfactory pretreatment to eliminate odors from effluents: lime or other

chemical neutralization followed by filtration; oxidation by use of hydrogen peroxide; use of excess chlorine, or chlorine compounds, followed by the addition of sulfur dioxide; neutralization by ion exchange; treatment with activated carbons followed by an agitation period and filtration. The following vapor operations decreased many of the process kettle odor problems:

Generous provision of Transite ducts fitted with condensation traps leading to: water-wash or spray towers fitted with baffles and coarse glass fiber; the same type of tower system fitted with an ammonia spray jet for highly acidic vapors; use of odor modifiers or "counter-odors" for localized areas; cylindrical air ozonizers; and finally, the various types of activated carbon adsorption towers. Counter-current treatment of the odor-ladened vapors was employed in all of the tower treatments.

Some of the legal aspects of odors in industry were mentioned.

ODOR PROBLEMS IN THE PAPER INDUSTRY

By Ernest Reed

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It is theoretically possible for paper and paperboard to be manufactured without an odor. It is further possible to fabricate the end products, such as containers, so that they are odorless. In fact, this is the rule rather than the exception.

When we say odorless, we really mean that the material does not have an *off odor* or *off taste*. This is especially true in the paper field. The expression *natural paper odor* is often used in describing odorless paper.

The paper industry has its odor problems, and some of these can be very serious and costly. Odor flare-ups occur sporadically and, more frequently than not, are unanticipated. The odor flare-ups are not anticipated for the very simple reason that causes of the odors have not been sufficiently studied nor adequately described.

Groundwood virgin pulp of any species may be so processed that it will have only what is referred to as the natural paper odor. Some species, such as hemlock, may be more troublesome than others. It may be assumed, however, that each species of wood has its own odor constituent when the tree is cut. There is some evidence for this. These odor constituents are chemical compounds and the ones from the different species may be so similar in structure that they come out of the mill processing the same, to the extent that they are no longer odorous. There is some evidence along this line.

Samples of two different ground wood stocks in the pulp condition were distinguishable by their odors, but merely by sitting in uncovered beakers in the laboratory for 12 hours, they became alike and were both characterized as having the natural paper odor. This indicates the possibility that oxidation eliminated odor constituents.

The introduction of the wood fiber into the mill system causes consideration to be given to the possibility of what might be called added sources of odor. The first of these is water with its many possible variables. Beginning with the beater, the ground wood and water, at the temperatures used, forms a perfect culture chamber for many kinds of organisms. These organisms may be Bacteria, Phycomycetes, Basidiomycetes, Fungi Imperfecti, Algae, or possibly Protozoa. What types are present at any one place or time is a matter, primarily, of the region and season of the year. One form may be dominant in one mill and another in another mill. One may be dominant in one season and another in another season. The populations of these organisms will vary in type in the same manner. Theoretically each organism is potentially a cause of odor, some more and some less. For this reason alone, control of these organisms becomes of great importance. There are, of course, other and more important reasons for controlling them, such as slime control. The present methods of controlling organisms, once they are present in a system, calls for germicides to be used; and once these germicides are introduced, they in turn become potential causes of odor. The extent to which these are troublesome as odor causes is affected by the control measures used in the mills. It is possible that the materials of sizing are a source of odor. General mill processing can be the cause of odors.

Provided with odorless paper as a result of adequate control of the aforementioned possible causes of odor, the conversion of the paper into containers introduces in some cases waxing materials, and these may be the cause of odor. Inks and dyes may also be the cause of odor.

Up to this point, we have been talking about paper which is made only from virgin stock.

Paper manufacturing operations are seldom confined to the use of virgin fiber. The clippings from all processing machines must be re-used and as they go back into the mill system, they carry with them the inks and dyes and any other added materials of the previously fabricated paper or paperboard. To the extent to which this re-run paper is used, the possibility of foreign odor's occurring is increased.

Then there is the great supply of scrap paper which comes into the mills from city collections and this, of course, is of various kinds, grades and selections, but it introduces many more variables as possible causes of odor. It also makes necessary the use of increased amounts of germicides because of the introduction of microorganic life with the waste paper.

It is in terms of details, such as we have mentioned, that the paper industry has odor problems. There are some odor problems, however, which become troublesome when paper is used for packaging different kinds of food. The customer buys a cake in a paper box and takes it back to the retail store and complains that it smells bad, or tastes bad—it may be the same thing—and the retail cake man goes back to the box company and complains that his box is at fault. The box man goes back and blames the paper man, whereas we have found in some of these cases that the fault lies in the food that went into the package. Certain materials such as bakery goods have more or less shortening which may be the source of odor when it is confined in a paper box. The same is true of candies and other materials which are frequently sold in paper containers of various kinds. So this becomes another category of odor problems which the paper industry must consider. It calls for good coordination between the paper box suppliers and the merchant packaging the food. To a much lesser extent, odors may be a problem in packaging other materials than food, but these may not presently be considered as of great importance. It is possible, however, that people will become more odor conscious and refuse to buy shirts that do not possess the right smell.

In considering an outline of the odor problems of the paper industry, one cannot exclude the problem of odor detection or identification. It has nothing to do, particularly, with paper, but with the human nose and the smelling faculties of man. I have tried odor-control studies on a roomful of paper men. They were to describe, identify, or compare the odors. From the result it is evident that there is no standard reaction and we are not equipped with what we might call a key to the different odors. This is one of our most troublesome problems. Furthermore, we must further be able to express odors in a quantitative way, or in a degree of intensity. We have set up such a method which we can use for our own purposes in the laboratory, but to have someone else duplicate our work somewhere else is quite another matter.

ODOR MODIFIERS

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This paper primarily emphasizes the application of essential oils and related material for the control and modification of undesirable odors.

Odor control includes:

(1) Elimination of odor by mechanical and physical means;
(2) By chemical means;
(3) By odor masking or modification with aromatic materials.

In the first method, odor-bearing substances are mechanically eliminated by washing or filtering, or by employing an absorbent such as activated carbon. In industrial plants these methods can be effectively employed for removing process by-products, thereby preventing dust, fumes, chemical vapors, and some odoriferous gases from reaching the atmosphere outside the plant, with the consequent diffusion of objectionable odors throughout the countryside.

Destruction by combustion of certain protein or vegetable materials, such as garbage, is practical only under controlled conditions. Certain oxidation products of nitrogen and sulfur, however, which may be evolved present hardly less of a problem.

Chemical treatment, where applicable, can control bacterial decomposition and the resulting odor. The hazard to human and animal life, as well as to plant life, leaves much to be desired in the way of control when formaldehyde, mercurials, cresols, acids, alkalies, and oxidizing agents are employed. It should be mentioned here that the quaternary ammonium chlorides have a wider application for odor control than those chemicals and they assure a certain effectiveness.

The aforementioned methods have had the attention of engineers and chemists with satisfactory results when applied to certain industrial and health problems. We can turn our attention for the moment to odoriferous products by stating that a fuel oil is no less valuable because of an objectionable odor and that the properties of solvents derived from petroleum lack nothing in usefulness as carriers. Inasmuch, however, as these are frequently handled by odor-sensitive human beings, it is highly desirable that the manufacturer who wishes his product to have a wide acceptance should be cognizant of its odor and the methods whereby the odor can be economically masked or modified.

We have at our disposal many hundreds of chemical compounds that exhibit odors in varying strengths and intensities, each having a characteristic note or nuance.

The essential oils are probably basic in the arsenal of the perfumer-chemist. An essential oil may be described as the volatile odoriferous oil usually obtained by steam distillation of certain plant materials. The essential oils should not be confused with the fixed oils or fatty oils such as cottonseed oil, olive oil, almond oil, tung oil, or with the animal oils and fats. Furthermore, they should be differentiated from mineral oils. The essential oils are not simple compounds but mixtures of volatile solids and volatile liquids, each of such components having a distinct chemical composition and boiling point. The odor intensity is dependent upon many factors, including the vapor pressure, temperature, and the nature of the chemical entity.

In addition to the essential oils, the perfumer-chemist has at his disposal isolates from essential oils. These components have a high odor intensity and, in many cases, superior diffusiveness; more so than when they occur in the essential oils from which they may be isolated. Organic chemistry in recent years has made it possible not only to synthesize a large number of the isolates of essential oils, but also odorous chemical compounds that had not existed heretofore or which could not be detected in the natural essential oils. Odor-stabilizing materials, or fixatives, as they are known to the worker with aromatics, are also of great importance. These may be of natural composition, such as balsams, gums, and resins, or they may be synthetic chemical compounds.

The art of the perfumer dates from ancient times, but it is only at the present moment that this art, wedded to the science of chemistry, is capable of producing not only new fragrances for the ladies' pleasure, but, even more important, this collaboration of art and science has opened a new approach to odor control. Much of the accomplishment in the recent past was the result of empirical knowledge and, while this experience still plays a very important role in the field of aromatic deodorants, laboratory control methods and field tests have been of great assistance in developing a new body of knowledge and techniques.

By combining the various aromatic materials and making use of the particular properties of the individual components, we can build a whole series of odor modifiers with an exceptional performance value.

The final phase of this brief discussion is best considered from the strictly practical viewpoint. A few examples may serve to illustrate the accomplishments in this endeavor. A properly formulated aromatic modifier will economically alter the objectionable odor in volatile solvents such as mineral spirits or methyl ethyl ketone. For example, Deodorant "X" costing $1.50 pound used at the rate of one pound in 500 gallons of mineral spirits will greatly reduce the objectionable odor. This is accomplished at a cost of 3/10 of one cent per gallon of solvent. The paint in which the mineral spirits so treated is used has increased sales appeal. A heating oil having an objectionable odor can be improved considerably with only a fractionable percentage of a low-cost aromatic modifier. Here the cost of improving the odor is calculated in pennies per drum, whereas refinement by fractionation or chemical treatment would be very costly in comparison to the selling price of the fuel. Synthetic rubber has many advantages over natural rubber and except for its odor could be used for many household and personal items. Here again, the perfumer-chemist skilled in technical odorization with aromatics can come to the fore with blends not only to mask the objectionable smell of the rubber, but he can also design aromatic compositions to impart an entirely new odor. The latter type aromatic compositions, when especially formulated for the purpose, can be employed to advantage in vinyl plastic fabrication either to mask an objectionable odor or to impart a characteristic and pleasing odor effect.

Whatever the requirement—to cover the odor or to change the odor—each is practical within the field of odor modification with aromatic materials.

There are other interesting and important applications of aromatic odor modifiers. Odors associated with certain types of diseases make working conditions difficult for physicians, nurses, and others who minister to the sick and, in addition, these odors accentuate the discomfort of the patient. An aromatic odor modifier formulated for the purpose will mask these unpleasant or nauseating odors for a prolonged period and will impart the effect of a freshly cleaned room to the air in the vicinity. The same types of aromatic compositions, through various methods of dispersion, are utilized by veterinarians to control animal odors. Even in large areas, such as zoos, the odor conditions are improved in an outstanding manner.

During World War II, the confined area of hospital planes was made more tolerable through the use of aromatic deodorants and today, even in commercial aviation, the pleasure and comfort of the traveler is enhanced through the use of aromatic odor modifiers.

By the extension of methods, odor control can be carried into public restrooms and theaters and can be introduced into air-conditioning equipment to control musty odors and to mask unpleasant smells.

We now have under field tests aromatics for improving the odor in industrial plants where odor conditions have been the cause of many complaints by the operating personnel; and there are, at this time, very promising experiments which may lead eventually to the elimination of objectionable odors which would otherwise be dispersed from industrial plants and incinerators into the surrounding area.

ODORS, ODORANTS, AND DEODORANTS IN AVIATION

By C. R. Spealman

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"Perhaps the most useful of all methods of detecting and estimating gases and vapors in the air is by their odors and irritant effects. Only a relatively few toxic ones are without either of these characteristics, notably among which is carbon monoxide."—Patty.[1] The presence of odorous or irritant substances quickly forces itself into consciousness; it is this speed and certainty of detection that is the basis for one of the main interests in these substances in aviation. The early, certain detection of toxic air contaminants (or other volatile materials which may indicate that some important component of the airplane has failed or is malfunctioning) is of special importance in aviation. An airplane must land if a serious situation has developed which cannot be remedied in flight. Time may then be a factor determining safety.

During the six months' interval from July 1 to December 31, 1952, there were 94 incidents in which air contaminants occurred in United States civil scheduled air carriers.[2] In most of these cases, the air contaminant was smoke arising, usually, from electronic or electrical equipment. There were also, however, several incidents of contamination with gasoline, oil, hydraulic fluid, and other chemicals. The presence of the air contaminants was detected quickly, generally by odor but sometimes visually, in the case of smoke; and, where necessary, the proper actions to meet the situation were taken without great delay. In the majority of cases where corrective action was necessary, it was of minor nature, such as disconnecting electrical connections. In 21 of the 94 incidents, however, unscheduled landings were made. Other actions taken to meet these situations included using protective oxygen breathing equipment and instituting emergency smoke evacuation procedures.

The above facts give some information as to the frequency of incidents in which the early detection of air contaminants may be valuable. A list of materials that can contaminate the atmosphere in an airplane follows:

a. ADI (anti-detonant injection fluids).
b. Battery fumes.
c. De-icing or anti-icing fluids.
d. Exhaust gases.
e. Fire extinguishants.
f. Hydraulic fluids.
g. Propellants (gasoline, rocket-assisted take-off, *etc.*)
h. Refrigerant fluids.
i. Smoke and thermal decomposition products.
j. Various chemicals which may be carried as cargo.

The importance of odor in the recognizing of the presence in the atmosphere of these materials has already been indicated. In fact, the general usefulness of odor in this connection is widely appreciated in aviation circles. For example, a recent newsletter published by a large aviation insurance company advises pilots that the odor of exhaust fumes means that carbon monoxide is present and indicates that proper actions should be taken to avoid the poisonous effects of that substance. The usefulness of odor in detecting the presence of dangerous air contaminants in airplanes is also shown by the desire to make non-odorous or slightly odorous materials detectable by adding odorous chemicals (odorants). Most work along these lines has been with fire extinguishants, but development has not proceeded to the point of practical application. With regard to the status of odorants for carbon dioxide fire extinguishants, we have recently received the following information from a representative of the Walter Kidde Company:

"The Naval Research Laboratory report does indicate that iso-amyl isovalerate can be considered for odorizing carbon dioxide, but to our mind, this does not have a sufficiently distinctive odor to warrant its use. For example, up to 3 per cent concentration, this material is hardly distinguishable from certain body odors, and is classed as having an odor of body perspiration or dirty socks. Obviously, this sort of indicator might be overlooked in some cases or, on the other hand, persons might be misled into worrying about carbon dioxide when, in fact, the odor originates from personnel.

"We have done considerable research work on our own to discover or develop a satisfactory warning agent. To date, all of those investigated have been found objectionable on one or more counts. It is, therefore, our belief that no suitable odorant is presently available and, furthermore, that greater safety can be secured by use of the oxygen mask, together with a discharge warning indicator."

The subject of odorants, however, continues to be discussed in aviation circles. The scope of their possible usefulness is indicated by the suggestion that distinctive odorants be added to all volatile materials used on airplanes.

Up to this point we have been discussing the usefulness of odors in aviation. We have, also, the problem in aviation of dealing with undesirable odors. One type of undesirable odor is that which comes from some harmless source but which is not familiar to the pilot. Cases have occurred in which pilots have made unscheduled landings or taken other unnecessary actions because of perceiving an odor which they could not identify. In these cases, the odor came from chemicals being transported as cargo. Possibly such occurrences could be avoided by briefing pilots on the odor and other properties of the substances being shipped. Another problem in this category results from odors arising from the body, from smoking, and from food preparation and the like. The control of odors in aircraft used to evacuate the sick and wounded presents similar problems. In ground installations, these odors are relatively easily removed by ventilation. In the modern pressurized airplane, however, it is difficult, because of limitations on weight of equipment, to provide an optimum supply of fresh air. As a consequence, the use of deodorants may be resorted to. Many of these contain formaldehyde, about which the late Doctor A. D. Tuttle of United Air Lines had this to say:[3]

"As a safety measure, the UAL Medical Department disapproves the use aloft of any air deodorizing spray containing formaldehyde or any other ingredient which is known to impair the sense of smell. It had to emphasize again such action only this year in the case of a deodorizing spray in which the manufacturer claimed that only a sufficient amount of formaldehyde was used in the formula to act as a preservative. Many of such products in the past used formaldehyde as an ingredient in clear recognition of the fact that its action on the olfactory nerve brought about a temporary paralysis or at least a serious impairment of the sense of smell which, of course, made the preparation containing formaldehyde, in any competitive tests run, stand out as a significant deodorant when compared with other preparations not containing this paralyzing ingredient.

"Laboratory tests and other practical tests clearly disclose the subjective effects on the sense of smell of any person breathing air containing formaldehyde. In our opinion, and as a result of our experience, any deodorizing air spray containing formaldehyde, even as claimed by a manufacturer in quantities only sufficient to act as a preservative, should not be used aboard aircraft. Any impairment of the sense of smell whereby members of the flight crew or even passengers could not early and quickly detect in the air the odors of burning, smoke, gasoline, or other foreign odors calling for an immediate search for and detection of the cause of such odors would invite a hazardous situation. Even when Passenger Service representatives, as they are apt to do, express the opinion that it would be 'fine' in the presence of foul air in the cabin to inhibit temporarily the sense of smell by using a formaldehyde product, they are prone to overlook the fact that the sense of smell as well as the sense of taste enters equally into the gustatory delight of the savory meals they serve aloft. However, for safety purposes alone, we should not permit crew members to be exposed to and breathe cabin or flight deck air containing formaldehyde or any other ingredient known to impair the sense of smell. I cite this case as another instance where the medical department of an airline must carefully investigate the ingredients of any air deodorant spray which a cabin service department may want to use. In any series of practical tests made, let us say among ten or more different kinds of air deodorants, the selection, based on our past as well as present experience, will invariably be the product which contains formaldehyde, because of its direct inhibitory action on the sense of smell. In my opinion, this item is of sufficient importance as to warrant it being brought to the attention of all airline supply departments and other departments concerned in the use of such deodorizing products."

There seems to be no doubt that developments in the science of odors and olfaction will be of importance in aviation. At the present time, the following aspects of odor and olfaction appear to be of special interest:

a. Odor classification. Interest here is in relation to describing and identifying odors and developing odorants.

b. Adaptation and masking. Interest here is in relation to identifying odors as well as in relation to preventing the perception of body odors and the like.

c. Anosmia. Interest here has to do with the development of effective tests for complete or partial anosmia.

Summary

(1) Odors are sometimes useful in aviation for detecting the presence of air contaminants which may be toxic or which may indicate malfunctioning or failure of certain equipment. In this connection, odorants have been proposed for use with some of the volatile, but relatively non-odorous materials used on aircraft, but to date no practical application of odorants has been made for this purpose in aviation.

(2) Odors from the human body, from smoking, and from food preparation and the like are a problem on airplanes because of limitations in ventilation capacity. "Deodorants" are sometimes used to prevent these odors from being perceived. Some of these "deodorants," although effective for the intended purpose, cause undesirable effects, such as, raising the threshold of the crew for perceiving odors and impairing the pleasurable "taste" of food.

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HOTEL ODOR PROBLEMS *

By Edward J. Kenney

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York Research Corporation, Stamford, Connecticut is the official technical consultant to the American Hotel Association. In this capacity, this organization tests many products annually and also answers a variety of questions in the field of institutional maintenance. A review of the files on hotel odor problems has shown that the majority of questions pertain to the control of mildew odors and those from lavatories. To a lesser degree, the A. H. A. membership has indicated interest in the problems of odors from kitchens, garbage disposal areas, and the control of stale smoke odors.

Mildew Odor

The problem of mildew odor is most troublesome to hotels in southern humid areas. In past years, this problem was particularly intensified by the increase in use of wall-to-wall carpeting. In many cases, it is completely unfeasible to remove wall-to-wall carpeting from the hotel for outside cleaning. This necessitated the shampooing of rugs on the floor. During the drying period, which in many cases lasted as long as 48 hours, mildew developed. The problem was further heightened by the fact that on-location rug shampoos were almost universally composed of soap. Soap residues provided food for mildew and contributed to post-cleaning mildew odor. As a result of an extended program on rug shampoos, York Research Corporation recommended to the A. H. A. membership, that soap shampoos no longer be used for on-location cleaning. Other scientific reasons stood behind this recommendation besides the fact that soap residues created an odor problem, the principal one being that soap residue causes carpets to resoil at a faster rate than normal. As a result of the study on rug shampoos, tests were devised to evaluate the better type of synthetic detergents for use in rug cleaning. The A. H. A. now maintains a list of acceptable synthetic detergent shampoos, which are recommended to its membership. These approved products meet the objections cited.

To combat odor developing from mildew growth on the backing yarns of a carpet, tests were performed on various mildewcides suitable as additives to rug shampoos. One such product has already been recommended to the A. H. A. membership and further work along these lines could be done.

For on-location cleaning of carpets, the recent development of an efficient dry-cleaning absorbent compound has been of great advantage in minimizing the carpet mildew odor problem. One product which has been approved for hotel use dries rapidly (30–45 min.) and does not wet out a rug or carpet. Improper use of even a good synthetic detergent can cause heavy saturation of a carpet with resulting prolonged drying time and increased susceptibility to mildew development in the backing yarns.

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* Prepared by the Staff of the York Research Corporation, Stamford, Conn.

Lavatory Odors

At present, lavatory odors are almost universally controlled by masking agents. The method of control may take the form of any one or more of the following: continuous evaporation of perfume material; odorized cakes in urinals and toilets; and frequent washing of floors and fixtures with disinfecting solutions, including pine oil and germicidal compounds of the phenolic type. Hotelmen have frequently expressed the opinion that the pine odorant incorporated in these products is almost as objectionable as the odor it is masking.

From time to time, there have appeared on the market ozone generating units claiming to control air-borne odors by the oxidizing action of ozone liberated by the unit. In general, such units have been relatively unsafe to use because of the lack of control of the ozone concentration developed in the air.

Another approach to odor control in lavatories has been the development of air circulating units employing cartridges filled with activated carbon. Such units, while sound in theory, have suffered the disadvantage of the necessity of re-activating the carbon in the cartridges and the initial cost of the equipment. Such units have not been studied by York Research Corporation in any great detail as yet.

Stale Smoke Odors

Another troublesome odor problem is that of stale smoke odors in cocktail lounges and other public rooms where curtains, draperies, carpets, rugs, and upholstered furniture are subject to tobacco smoke for prolonged periods of time. The odor is especially pronounced after such a room has been closed for several hours; for example, after the period of closing of the lounge until the following morning when work is begun to prepare the lounge for the next evening's trade. Aside from odor-masking perfume materials and activated carbon units, there is little available to combat this problem. What is needed is an effective, inexpensive means of minimizing the intensity of the odor during its generation and, also, a product to effectively deodorize curtains, upholstered furniture, *etc.*, which have been exposed to high concentration of tobacco smoke. Such a product must not affect the fibers or the dyes of the textile, nor should it leave a residue which would cause the textile to attract and hold dirt more than it would normally.

Kitchen Odors

Kitchen odors have been largely overcome in hotels by the use of modern ventilating hoods over the cooking units. Odors in garbage disposal areas, adjacent to kitchens, represent a negligible problem in a well-ordered kitchen, since refuse is promptly disposed of and all containers are periodically cleaned with detergents followed by a disinfecting solution.

General Remarks

In general, most deodorants offered for sale in hotels are merely odor-masking and not odor-killing agents. Certain quaternary ammonium compounds have been effective in spot-wise application to control localized odors. Many of these surface active materials actually destroy an odor rather than mask it, since the quaternary ammonium solution is odorless. Devices which can effectively kill odors on a continuous basis should find a wide market in hotels.

ODOR PROBLEMS IN FEDERAL OFFICE BUILDINGS

By W. E. Reynolds

Commissioner, Public Buildings Service, General Services Administration, Washington, D. C.

In Federal buildings under the jurisdiction of the General Services Administration, we are primarily concerned with people, with providing in the buildings working conditions that will produce the greatest return for the taxpayers' dollar. We are keenly aware of the responsibility to provide, for example, the most effective lighting and space conditioning and to construct buildings with materials and equipment that mean low operating costs and low annual maintenance.

Working situations are viewed from many angles and, depending on the source of greatest pressure, are usually defined in terms of a particular treatment. We try to meet this problem by developing a set of standards that have the greatest application in performing Government business efficiently and economically.

Standards that deal with size, shape, and location of a Federal building; standards that concern architectural, structural, and mechanical features, materials, and equipment are of prime interest to us when planning, constructing, and managing the public buildings.

How does this concern the subject of odors? Possibly we have not given the subject its proper emphasis when developing the standards for guiding the mechanical design. We are, however, acutely aware of the problems that confront us as I shall illustrate by citing some of our experience.

I am greatly impressed with the scope of the papers in this monograph. We have not engaged in, nor do we plan to institute, a basic research program that will treat solely with the odor conditions found in public buildings.

We must rely on the research effort and findings of such a group as this to assist us in getting the right answers to our operating problems and to influence the revisions in our design standards. Reporting our experience and stating some of our requirements to you may serve as laboratory material and stimulate the research-minded to develop new methods for attack and to show up any weakness in our present methods used for eliminating objectionable odors.

I was somewhat surprised, when I sought material for this paper, to learn how little we have scratched the surface of this subject. I do not believe I can mention any new experience for you, but I can relate some of the problems we have faced and report on the steps we have taken, and plan to take, when confronted with odor control and odor elimination.

In many of our large office buildings we have cafeterias that meet the food requirements of four to five thousand people for one hot meal a day. The cafeteria may be located on the ground floor, but in a number of cases, such as the Pentagon Building and the new General Accounting Office

Building in Washington, it is located on one or more of the upper floors. The two cases cited are fully air-conditioned buildings. We have buildings which are not air-conditioned that have similarly large cafeterias. Each has the same requirement, to prevent the cooking odors from permeating the office spaces. When one is hungry, the odor from cooking may be most pleasant but, like perfumes, a little goes a long way. Under certain operating conditions and under atmospheric conditions in non-air-conditioned buildings, our management people have a troublesome situation on their hands. The method of removing the cooking odors from the cafeteria space by introducing into the space a sufficient number of air changes and then ventilating to the roof by way of the exhaust hoods is an expensive one. It is more expensive when the space is air-conditioned because no conditioned return air can be utilized. Considerable savings will result, not only in design and construction costs, but in operational costs, when a way is found to control or eliminate the odors at the source and to dispense with the special air-conditioning or ventilating systems.

We have several small cafeterias or dining areas where the conditioned air is recirculated. This is accomplished by using adsorbent or activated carbon filters built into the return air ducts. The method, however, does not suit the larger cafeterias because of the high maintenance costs of replacing the material presently used in adsorbent type systems.

Turning from cooking odors which may be classified in a general sense as pleasant, we find we are usually concerned with unpleasant odors. In designing the fully air-conditioned office spaces, the designer finds he is unable to meet the conditions later imposed on the equipment because of the constant tenant changes that occur within a building when the building is fully occupied. Whether the assumption is made that the space will be completely partitioned for office use or only certain areas will be partitioned, it is a foregone conclusion that the areas selected for general or special conditions will not suit the organizational planning of the tenant assigned to the space. The changes in occupancy usually are called to the attention of the building superintendant because the occupants are either too hot or too cold when first assigned and adjustments are needed at once. The hot or cold complaints can usually be corrected after some study by the operator; but when the complaint is too much carbon dioxide, not enough oxygen, staleness or stuffiness in the air, too much tobacco smoke remains in the area, or a heavy odor of perspiration is deeply disconcerting to the occupants, then the operator is in trouble.

We call upon the services of the Public Health Service when the room complaints concern the quality of the air and its composition. We have not found a condition to exist wherein the air supply was dangerously deficient in oxygen or where there was an excess of carbon dioxide. Complaints of this nature are never ignored, and we are of the opinion that considerable research may be needed to correct satisfactorily a situation that causes complaints of this kind.

There is a theory that air particles lacking an excess of negative potential may produce a condition in some people that is debilitating while, conversely, if the air particles have an excess of negative potential they will cause a feeling of well being. If this is correct, it may provide one of the tools needed to meet a condition that is referred to by occupants as deficient fresh air supply. Our present means for measuring this condition is unsatisfactory because the instruments used by the operator do not record the air particle characteristics. There are devices on the market, for small scale application, that generate negatively charged particles. Devices using this principle, so far as I know, have not been applied to large air-conditioning systems.

Rest rooms are designed and constructed in our buildings to meet the most advanced requirements of the plumbing codes; if practicable, to introduce features that spell better servicing and improved sanitation; and to encourage cleanliness on the part of the users. There are, however, in older installations inherent odor problems that must be eliminated. We believe most odor problems that are thus encountered can be reduced to a minimum of annoyance by servicing with the proper detergents and chemicals. This is not the complete answer. In searching for it, we have examined some devices that give off ultraviolet rays that break down the air and provide nascent oxygen which, if intelligently used, may impart a sense of freshness to the areas. Because modern design locates rest rooms well within the buildings, they are dependent on independent exhaust systems serviced by an adequate air supply coming from the corridors. There is still much to be gained by continued study in this field of odor control.

Unpleasant odors affect employees in varying degrees. We have found that painting in areas adjacent to office workers is particularly annoying to women. They sometimes insist, with the assistance of top side, that the space being painted be isolated to a degree that is not only expensive but often impracticable to accomplish, with the result that the work is scheduled and performed when overtime payments are required. Our approach to this problem with the viewpoint of economy, is to use interior paints that are practically odor-free or odor-masked. Our painters are finding them desirable and occupants observing the painters working are often interested enough to ask the nature of the paint that is no longer offensive.

The paints so classified for interior work are an alkyd resin water emulsion type, a latex emulsion type, and an alkyd resin flat. These paints have been developed within the past fifteen years and the principal improvements have been in the drying time and the odor reduction. The odor reduction, to a degree, has been accomplished with masking agents or with the use of the so-called odorless solvents. For our viewpoint as operators of public buildings, the greatest benefit lies in the fact that the paints are no longer obnoxious or nauseating to the tenants of the adjoining spaces.

We are all familiar with odor sources such as rugs and upholstery, leather and plastic, usually found in the executive-type offices. Here again we are called upon, at times, to mask the odors from furnishings of this kind until the newness has disappeared. I have observed the subject of one of the papers in this monograph is entitled "Odor Modifiers" and the application of the principle should prove very helpful to us.

I have not touched on odor sources that are troublesome periodically, such as dead rats located in inaccessible space, grease traps, garbage rooms, laboratories, and shop areas, because the problems are either local or special and the remedy is removal, improved sanitary practices, additional ventilation, or special design requirements.

I mentioned previously the use of activated carbon filters, or adsorbers, to remove cooking odors from the air supply that would affect the tenant space. Additional examples of their use in connection with office space in Washington are:

(1) The Pan American Institute Building where the filters are used to prevent motor exhaust fumes from entering the building which is fully air-conditioned and draws its fresh air supply at the street level and the roof level. The building is located adjacent to a street where the buses twice a day wait for and discharge large numbers of federal employees.

(2) LaSalle Building. Office space was provided in a windowless area where it was practically uninhabitable because food odors from a near-by restaurant permeated the space. The space was air-conditioned and the fresh air intake supplied with odor adsorbent filters.

"Stuffiness" is usually associated with the "bad air" complaints and is particularly the complaint that the superintendent of an air-conditioned building receives in the midafternoon. It is usually not a condition that is widespread in a building. It may be found anywhere in the tenant space but usually where the space has been cut up with partitions. It may be one or a combination of three factors that causes the complaints. They are identified as air movement, humidity, and temperature. As mentioned previously, the space assignment pattern selected by a tenant for conducting the Government business often upsets the planned functioning of the air-conditioning system. Only in extreme cases will the tenant permit the changes in partitioning or the relocation of the equipment used in the tenant's operation in order to conform to the designed conditions. The result is that readjustments are made to the system in attempting to correct the condition.

It has been observed, and it is our judgment, based on operating experience, that the relative humidity in office space should not be permitted to exceed fifty per cent regardless of temperature maintained. When this factor and the temperature are controlled properly by the operating engineer, the odor, or "stuffiness," complaints are greatly reduced. There are other conditions where air movement has been restricted by tenant actions in blocking return air grilles; the complaint also is "stuffiness." These complaints usually occur between 2:00 p.m. and 3:00 p.m. When the operator lowers the temperature only slightly, the tenants are generally satisfied. Too much food for lunch may be the chief contributing factor in the discomfort of the occupants at this time. Complaints of "stuffiness" may occur also when conditions are normal in the system and there has been no rise in temperature or humidity, or a change in air movement in the space. Again, lowering the temperature slightly satisfies the occupants. We are hopeful that "stuffiness" or "bad air" complaints may be eliminated entirely in office buildings when the following design conditions are permitted to be effective in the tenant areas: a movement of air of not less than one and a half changes of outside air per hour; not less than fifteen C.F.M. per person of outside air; and not less than twenty-five per cent outside air in a unit of conditioned air supplied to the space. A deficiency in any one of these requirements, which we consider to be minimum, definitely contributes to the condition of "stuffiness." It must be remembered that temperature and humidity are the other contributing factors that must be controlled and may be equally as important.

This monograph shows how broad and varied is the odor problem in industry. I have touched on the principal tenant odor problems in the federal office buildings that we have experienced. I have not touched on odor problems associated with the special-purpose buildings such as hospitals, clinics, and laboratories. In general, the odor problems thus encountered are taken care of by means of special and adequate ventilation. This is a large field to explore and I am sure new methods will be developed to eliminate or control odors found in the types of buildings we are responsible for designing, constructing, and operating, and to do the job economically and efficiently.

In suggesting a guide for evaluating a system or method for controlling or eliminating odors in buildings primarily built for performing Government business, I believe these factors are important:

(1) Low initial cost;
(2) Low operational cost and low maintenance cost;
(3) Adaptability to existing equipment;
(4) Being as nearly automatic in operation as is practicable;
(5) Eliminating in operation a wide range of objectionable odors ordinarily encountered in space assigned to personnel.

B. Problems of Odor Research from the Viewpoint of the Scientist

PHYSIOLOGICAL PROBLEMS IN ODOR RESEARCH

By Lloyd M. Beidler

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Introduction

The consideration of the physiological processes involved in olfaction have stirred the imagination of men for many years. The mere fact that a living system is able to detect certain substances in concentrations of the order of magnitude of 10^{-13} molar is indeed remarkable. The additional fact that it may distinguish such substances from others whose molecular architectures are very similar is incredible. The study of the sense of smell by the physiologist is timely since both the border fields of biochemistry and biophysics suggest new approaches to the problem. It is also true that there is at present a considerable emphasis by biologists on the study of the interactions of molecules with living systems.

Some Physiological Problems of the Olfactory Process

The physiologist searches for the answer to the question: How is it possible for a group of olfactory cells to detect very minute concentrations of substances foreign to its environment, and how do the cells differentiate one substance from another? To understand the real meaning of this question, let us discuss some of the physiological events that take place in the olfactory system. The block diagram of FIGURE 1 indicates some of the major events.

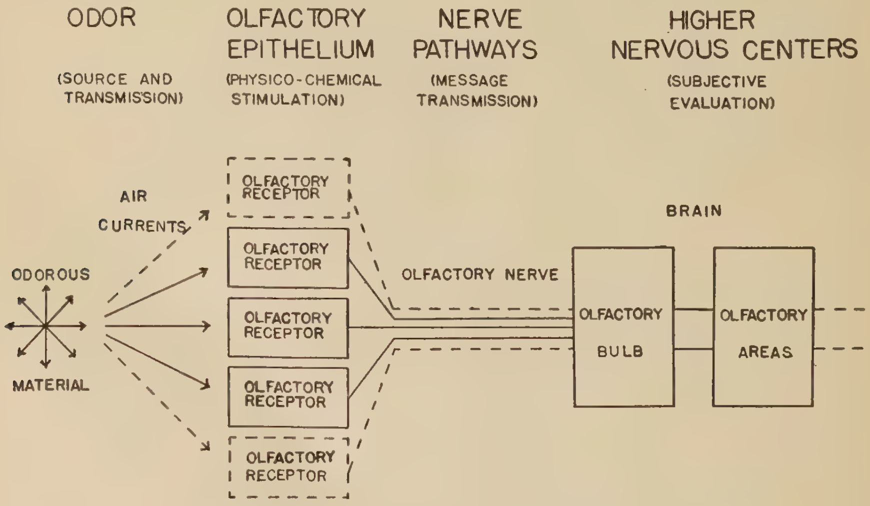

FIGURE 1.

Transmission of odors to receptors. Solid or liquid odorous substances must be volatile enough so that some of the substance is given off in a gaseous or vapor phase. This is then carried to the nose by air currents. Since much of the air currents do not reach the olfactory epithelium during normal breathing, a sniff is used to increase the air currents and create eddies that bring the odorous material to the neighborhood of the receptors. In addition to the eddies, it may also be necessary for the molecules to be transported a short distance by actual gaseous diffusion. Authors have suggested[1] that the difference in diffusion rates of odorous molecules may be a very important factor in odor stimulation. Adrian[2] has indicated that the varying rates of air flow in various regions may account for differences in the patterns of excitation in the olfactory organ itself. The receptive surface of the epithelium may be covered by an aqueous mucous so that the substance must also dissolve and diffuse through this aqueous phase.

Very little is actually known of the aerodynamical properties of the nasal passage, although the importance of the air flow in olfaction has been long realized. Recently, Jones[3] has shown that the measure of olfactory thresholds is very dependent upon many of the aerodynamical functions, particularly pressure. This is true to such an extent that thresholds measured with the common air blast techniques cannot easily be compared to thresholds measured by other methods. It is also known that the mucous covering the olfactory epithelium is constantly moving, but its importance in odorous detection is not clearly defined. A thorough study of the functional properties of the nasal passage should be undertaken by the physiologist.

Properties of the Olfactory Receptors. The olfactory area in man is about 2.5 cm^2 and contains a large number of olfactory sensory receptors which are supported by sustentacular cells. The distal ends of the receptors terminate in small hairs 1–2 micra long and about 0.1 micron in diameter. These hairs protrude between the surrounding sustentacular cells and project into the mucous covering of the nasal cavity. The epithelial surface of the olfactory region contains cells that may have as many as 1000 hairs per cell, so that the free surface is increased tremendously.[4] The proximal ends of the olfactory receptors are small, unmyelinated nerve processes which form the nerve fibers that pass through the cribriform plate and enter the olfactory bulb.

It is believed that not all the olfactory receptors respond to odorous stimulants in the same manner. For example, some receptors would respond to certain odors but not to others. In this manner the receptor surface could distinguish one odor from another and thus man may perceive different odor qualities. Although it is certain that there are different functional types of receptors, they have not been identified histologically to the present time. For this reason, new attempts should be made to classify the receptor types morphologically. One method found to be successful in other areas of physiological research is the differentiation of cells by their chemical constitution. Since special enzymes may be involved in olfactory processes, it is worth while to attempt enzymatic localization in the olfactory area. Recent work by Bourne[5,6,7] has shown that certain enzymes are localized in the olfactory region. It would also be interesting to know the relative concentration of the enzymes concerned with cellular respiration, phosphorylation, and the acetylcholine system of the olfactory area. The concentrations of these enzymes might offer a clue as to their importance in the normal functioning of the olfactory receptor.

The determination of the number of different functional types of receptors and the properties of each is of utmost importance in odor research. This information would form a basis for the study of odor qualities which might ultimately lead to a suitable classification of all odors. It would also be basic to the study of the mechanisms involved in the stimulation of the olfactory receptors by various odors. At present, one studies these mechanisms only very indirectly by observing the total behavioral response of the organisms to a number of odors. Since many different types of receptors may be stimulated by any one odor, it is also imperative that physiological methods be developed for the study of the response of a single olfactory receptor.

A knowledge of the physiological properties of the individual olfactory receptors is needed before a satisfactory theory of odor stimulation can be composed. Not only should threshold values be determined, but also the quantitative responses to a large number of odorous substances should be studied in detail. It has already been found[8] that the taste chemoreceptors are not stimulated to the same degree by all substances, no matter what concentrations are used. A saturation level of response is attained where an increase in the stimulus does not result in an appreciable increase in the response. The magnitude of the saturation levels vary from one taste substance to another even though each of the substances may stimulate the same type of taste receptor. It is a common experience, also, with the sense of smell that two odors of similar quality may differ in intensity when both substances are applied at very high concentrations. It would be expected that the magnitudes of the olfactory saturation levels of single olfactory receptors stimulated by various odors would be directly related to the stimulating property of the odorous substance itself. This type of physiological information would contribute much to the determination of the nature of the odorous stimulus.

The ability of a substance to stimulate the olfactory receptors depends upon both the volatility and the threshold. The substance must be appreciably volatile so that it may be present in the air in a sufficient concentration to attain a threshold value in the vicinity of the olfactory epithelium. Although the threshold value may be independent of the volatility, it is dependent upon both a particular, as yet undetermined, physicochemical property of the molecule and the characteristics of the olfactory receptor itself. Many believe that if the physicist or chemist could design a method of controlling and measuring the concentration of the odorous substance, the ultimate nature of the stimulus would be forthcoming. The experience with taste receptors, however, strongly indicates that the problem is more difficult. In the study of taste, the experimentor can adequately control and measure the concentration of the solution applied to the tongue. In addition, the chemist knows more concerning the properties of inorganic salts and acids than any other class of compounds. Yet, there has emerged no satisfactory theory of salt stimulation of the taste receptors, and the particular physicochemical properties of these salts that are responsible for the stimulation are not known. The reason is simply that the nature of the stimulus is very dependent on the nature of the receptor. One must study both the physicochemical properties of the odorous substances *and* the physiological properties of the olfactory receptors.

The possible mechanisms that may be involved in the stimulation of olfactory receptors are so numerous and complex that every bit of information available should be used in its study. Not only magnitudes of responses and threshold values should be measured, but also other physiological parameters such as those of adaptation, fatigue, prolonged discharge, latency of stimulation, *etc.*, should be studied. It has already been noted by Adrian[2, 9] that the rate limiting step in odor adaptation is not in the olfactory receptors but in the neural components of the olfactory bulb. Adaptation plays such an important role in our olfactory experience that its physiological basis should be investigated further.

An important physiological technique used extensively in the study of biological systems is that of changing either the internal or the external chemical environments of the cells and then observing the change in cellular function. This is of particular value in the study of olfaction since it is known that when either hormones or certain chemicals are added to the blood stream, changes in the condition of the receptors occur. Internal perfusion by way of the blood stream offers an advantage to the experimental approach to these problems.

After the receptor is stimulated by the odor, there probably takes place an eventual electrical depolarization of the proximal end of the receptor which, in turn, initiates a series of nerve impulses. These impulses are electrical in nature so that they may be measured with appropriate electronic equipment. As the stimulus increases in intensity, the number of nerve impulses per second traveling down the nerve fiber also increases. One may say that the nervous system uses a form of frequency modulation to convey information over nerve fibers. A large number of nerve fibers converge on individual mitral cells in the olfactory bulb so the information relayed on from these mitral cells is dependent upon the information derived from the responses of a large number of individual sensory receptors located in the olfactory epithelium. The neurophysiologist would venture to guess that many of the phenomena of olfactory inhibition and enhancement occur in the higher nervous centers such as the olfactory bulb. It is also thought that molecular competition at the level of the receptors might occur. Electrophysiological studies of the nerve patterns arising in both the receptors and the olfactory bulb would provide information necessary to the better understanding of these complex interactions.

Objective Methods of Study

The above account indicates some of the problems that confront the sensory physiologist interested in the neural events of olfaction. Much emphasis was given to the objective study of the responses of single olfactory receptors to odorous stimulation. What physiological methods are available for such investigations? Experience in other fields of sensory physiology[11,12] suggest that such problems are best solved by recording the electrical nerve impulses from a single olfactory primary neurone as various odiferous substances stimulate the olfactory epithelium. Although physiologists may generally agree on this method of solution of the basic olfactory problems, none has succeeded in such a study using a mammal. The olfactory nerve is usually very short in length and inaccessible so that nerve recording is difficult. The individual olfactory nerves are also very small in diameter so that the electrical nerve impulses are small in amplitude. The olfactory area of the opossum, however, is sufficiently large so that many of the olfactory nerves must traverse a reasonably large distance from the olfactory receptors to the entrance of the cribriform plate. It is also possible to expose these nerves without interfering with the normal nasal passage. The technical difficulties involved in recording from single unmyelinated fibers remain, however.

Several physiologists[2,10,13,14] have attempted to study the olfactory processes by recording the electrical nervous activity from the higher nervous centers such as the olfactory bulb, olfactory tract, *etc*. These studies do not result in the same type of information one desires to obtain from the individual receptors. The nerve messages become very complex as they converge on the mitral cells of the olfactory bulb, for example, so that analysis is more difficult. Adrian[2] has suggested, however, that many odors excite different areas of the olfactory bulb so that each odor results in a different spatial and temporal pattern on the olfactory bulb. If this be true, then simultaneous recording from a large number of electrodes placed over the area of the bulb would allow one to study these patterns in detail. The techniques devised by Lilly[15] for cortical recording may be adapted for such a study.

Conclusion

The difficulties encountered in the study of the response of the olfactory receptors to odor stimulation hinder the sensory physiologist in his attempt to solve the physiological problems related to olfaction. There also appears to be a lack of interest in the sense of smell among biologists and other scientists. For these reasons the physiology of the sense of smell is relatively unexplored as compared to the senses of vision or audition. It is hoped that in the future there will arise enough interest and support in olfactory research so that more scientists will explore this virgin field.

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PROBLEMS OF ODOR RESEARCH FROM THE VIEWPOINT OF A PSYCHOLOGIST

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As a psychologist, I have been asked more than once what psychologists can do to help solve the mysteries of odor. It is hardly necessary to outline the area of psychology. Its problems are, most simply, those of discovering the basic stimulus-response relationships underlying the complexities of human behavior. There are, then, all the many behavioral aspects of olfaction which might prove challenging to psychologists.

The fact is that they do not prove challenging to more than a handful of research workers, as I have recently been reminded in preparing an article on the chemical senses for next year's *Annual Review of Psychology.* Less than five papers by psychologists have appeared in the last year. Probably one of the main reasons that there are so few well-substantiated facts and fruitful hypotheses is the scarcity of systematic investigations. This is undoubtedly partly attributable to the difficulty of working with olfactory stimuli since their crucial features are not known.

Psychologists are not alone in recognizing the basic problems of odor research as knowledge of the stimulus and how it functions, and provision of suitable apparatus for controlling it. We need to know the ultimate description of the stimulus. Psychologists feel that their training does not equip them to solve these problems as readily as the physical scientists, but they recognize their extreme importance. Some have even done a considerable amount of work on them, especially in the development of apparatus. For example, the method of blast injection as originally described by Elsberg has been viewed suspiciously[17] and greatly modified.* Several of us have abandoned pressure and volume as stimulus variable, preferring to hold them constant while manipulating stimulus concentration in some other way. Unfortunately, there have been no recent publications by psychologists on these modifications. The news is transmitted by word of mouth or in such gatherings as the ONR Conference on Chemoreception held at the Johns Hopkins University in 1951, from which came no complete printed report. A recent paper by Jones[7] emphasizes the lack of direct comparability between thresholds obtained with the technique as originally used by Elsberg and those obtained by some form of varying the concentration of the odorant. Some data which I have collected recently strongly suggest that stimulation by means of a blast, even when pressure is not varied, does not reveal as keen sensitivity as stimulation by means of a natural sniff. It is not inconceivable that we might be better off today if

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* Throughout this paper, references are given to sources which, in many cases, serve merely as examples of the point discussed here. The references are not necessarily in olfaction, but all are in psychology.

Elsberg had never publicized his creation, but it seems to me that the very eagerness with which it was adopted bespeaks the urgency of the need for stimulus control.

Many problems of the stimulus, however, we should like to leave with workers in other fields. The need which psychologists are especially trained to fill is for experimental procedures which insure collection of reliable and meaningful data. One of psychology's tasks has been to devise techniques of scaling perceptual responses so as to reduce "subjectivity" and, hence, the error of measurement as well. It is not hard to detect an uneasiness in nonpsychologists when they feel forced to rely on the responses of other human beings for their data. Perhaps it is necessary to remind them that our present understanding of vision and audition, those accepted examples of a reasonably well-understood sensory modality, was gained from data of precisely this nature, collected under standard conditions and with appropriate control of the stimulus. The decibel scale and the Munsell system of color notation, both highly regarded as standardized scales to be used by anyone somewhat in the manner of a yardstick, are both based on that most subjective phenomenon, the just noticeable difference. Descriptions of the development and techniques of such methods and of their applications run through much of psychological literature. A few selected references have been included here.[5,13,14,15,16,18]

I submit that the problem is not the subjectivity of the response but rather the inability to specify the stimulus and the lack of a uniform language of olfaction. We are still bedeviled with the stimulus error here; that is, the necessity to describe the odorous sensation in terms of stimulus objects. So, a given odor is called "like a rose" or another one "like new-mown hay." Suppose the variations of the color we know as yellow could be described only as "like certain roses" or "like new-mown hay"! If a workable vocabulary could be devised, a large portion of the "subjectivity" problems would automatically fade away. In auditory and visual experiments, one solution has been to avoid words by having the subject match his experience with one of a variety of standards provided. For example, if he is mixing two complementary colors such as blue and yellow lights in a certain proportion, he tells us how the resultant appears to him by manipulating white light in combination with either blue or yellow if necessary until the two mixtures look the same to him. Thus, without requiring words, he externalizes an internal event, making it available for quantitative measurement. Perhaps a similar approach can be exploited with odors. Another possibility which might prove helpful at our present stage of development would be to assign nonsense names to our stimuli rather than the names in regular use. At least, this would eliminate some of the diversity of meanings which different individuals attach to the same common name. Here psychologists can make a crucial contribution.

In addition to these general matters, the problems in psychology's domain are directed toward a discovery of the laws which describe man's olfactory behavior. The problems are so numerous and so varied that I have tried to classify them for this meeting in very general terms according to the type of psychologists who would typically be interested in them.

Considering first the physiological psychologist, or, as he is sometimes called, the sensory psychophysiologist, we can make a long list of questions he would like to answer. His goal is to give a complete description of olfactory sensation so he concerns himself first with olfactory thresholds, absolute and differential. Measurement of thresholds involves comparisons among substances, especially in reference to olfactory theory, and comparisons among methods and procedures of measurement. A lot has been done on this problem, but much of it is not directly useful because the units of measurement vary widely and are frequently incommensurable. Also, the odorants used have often been unidentified compounds or impure materials.[6,19] The study of mixtures is a second important topic that would interest physiological psychologists. What data we have on mixtures are skimpy and in disagreement. Claims are made both for a cancellation effect, analogous to mixtures of complementary colors in vision, and for the nonexistence of this effect. Absence of a vocabulary for odors complicates especially the interpretation of mixture results.[3] A third problem is that of adaptation, or olfactory fatigue. This phenomenon is well known to anyone who has encountered a strong smell that seems almost unendurable. A few minutes later it is almost, if not entirely, unnoticeable. Aside from the fact that it is worth studying because it is such a nuisance when working on other things requiring relatively long waits between stimuli, results from studies of selective adaptation should give some promising ideas for theory. The change in sensitivity is quite specific, affecting only the adapting stimulus or a few other substances as well. What is there in common among the substances in one adaptation group? As a fourth set of problems, there can be mentioned those of neural functioning and receptor action which fall into the physiologist's purview as well.[10]

Beyond all of the above questions, there is a wealth of specific problems which await other psychologists. The comparative psychologist would be interested in the same topics listed above when referred to nonhuman forms. He would like to collect comparative data on all aspects of olfaction for animals other than man, the purpose being to correlate function with structure in describing phylogenetic trends.[11] For the social psychologist, the problems are those of the effects of odors on group relations consisting of interpersonal contacts.[8] The learning theorist could use odors as stimuli in conditioning and learning experiments. This group of psychologists is a rapidly growing one since learning is recognized as fundamentally important in explaining human behavior. Many perceptual phenomena can be understood in terms of previous learning.[2,4,9,12] From the viewpoint of the clinical psychologist, the main questions are concerned with abnormalities in olfactory sensation such as hallucinations, the ability of odors to evoke early childhood memories, possible therapeutic uses of odors, changes in sensitivity with age, and others of this nature. Finally, for the applied psychologist,[1] perhaps working in industry, there is an endless assortment of practical matters which must be considered, including evaluation of preferences, acceptance and rejection thresholds, deodorization, consumer acceptance as a function of product odor, the effects of odors used in advertising, and so forth.

These, along with many more, are the things psychologists could do. In my opinion, they would do some of them if they were given the double impetus of improved stimulus control and increased publicity about these problems. This monograph can certainly contribute greatly toward publicity; let us hope that it will speed up realization of the first goal as well. I predict that if the nature of the adequate olfactory stimulus were discovered and publicized this spring, by next spring a crop of psychological doctoral dissertations in olfaction would be scenting the air and a great flowering of latent interest would begin.

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PROBLEMS OF ODOR RESEARCH FROM THE VIEWPOINT OF THE PHYSICIST

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Several theories have already been suggested to "explain" the mechanism of odor detection; many more will undoubtedly be forthcoming. It becomes necessary, therefore, to evaluate such explanations critically and to extract those ideas which are in accord with the facts. To do so, one must use objective experimental techniques which are capable of giving us reproducible results. The selection of such methods, to be sure, is never an easy task and is all the more difficult when dealing with so variable a subject as the living animal. Yet, such objective measurements will have to be made in this phase of biology if we are to understand "smell."

From the point of view of an instrument designer, the problem of odor detection in a broad sense exhibits three interconnected components:

(1) The *source or generator, i.e.,* the environment containing the odor substances;

(2) The *detector or sensing element, i.e.,* the physiologically active membrane or "nose" of the animal;

(3) The *converter-recorder system, i.e.,* the system translating membrane phenomena into brain responses.

It is obvious that these component systems are intimately interconnected. Their interactions as well as their individual characteristics must, therefore, be carefully considered. Such a subdivision into components is worth while in pointing out differing experimental techniques which are at present available or adaptable for study of these differing component systems. There are many experimental devices and procedures used in the fields of physics, chemistry, engineering, and biology which are applicable to the study of odor. We shall attempt to survey some of these techniques and their possibilities in furthering odor research.

The problem of producing an environment containing a known constant concentration of any desired odoriferous substance does not, at first glance, appear very difficult. When the requirements of such an environment are considered, however, we may be less inclined to dismiss this as an easy problem. Any one (or several) of thousands of odorous substances may be used; these may be gases, liquids, or solids; their concentration may range from one part per thousand to one part per ten million of air; uniformity of composition must be maintained; controlled temperature and humidity may be required; rapid changes in composition may be useful; adequate circulation of environment may be desired—many or all of these requirements may be essential. The interesting point is that most of these specifications may be met through use of techniques from the field of physical chemistry, especially that branch known as "gas kinetics."

Two general methods are available for preparing gaseous mixtures: the *vapor pressure saturation* method and the *flow mixture* method. The first takes advantage of the fact that the vapor pressure of any given liquid or solid is constant at any given constant temperature. Thus, if air is drawn or blown through a substance at a constant rate which is slow enough to allow the air to become saturated with the vapor, one can obtain very reproducible concentrations of the substance in the air flow. Concentrations less than the saturated vapor may be obtained by controlling the rate of flow of the air through the substance. One common example of this technique is in the humidification of air, where the air is blown through water kept at a desired temperature.

The flow mixture method provides means for a gas stream of the vaporized odorous substance to flow into and intimately mix with a flowing air stream. The composition of the resultant mixture is controlled by controlling the relative flow rates of the two gas streams. This method can be extended to mixtures of more than two gases. In order to obtain reproducible, constant mixtures, it is essential to have good pressure and flow controllers to maintain constancy of these factors in the mixing gas streams. Fortunately, a number of such devices have become available during the past few years and one can obtain a steady flowing stream of controlled composition containing odor substances plus air circulating in a constant temperature, controlled humidity test room.

Other, more specialized means are also available for producing smokes, mists, fogs, and solid particle suspensions.

It is not sufficient to prepare controlled atmospheres for experimental study. One must be able to check their composition. While the wide spread in "normals" responding to odor stimulus may be of such magnitude as to require relatively low accuracy of analysis, the study of response of any *one* individual to *changes* in concentration of odor substance will undoubtedly necessitate determinations to a much higher degree of accuracy. Thus, the analytical instruments must be sensitive to traces and must be able to determine such traces accurately. Furthermore, they should be able to analyze a wide variety of mixtures. This latter requirement is particularly important in studying "uncontrolled" atmospheres such as are found in storage vaults, public places, tunnels, *etc.*

A number of instruments meeting these basic specifications have become available recently. The most versatile of these is the mass spectrometer. This instrument is able to analyze, with a high degree of accuracy, a sample of gas for traces of substances as low in concentration as parts per million. The gas sample is introduced into a continuously, highly evacuated mass spectrometer tube. This latter contains a hot filament which emits electrons, as in some of the familiar radio tubes. These electrons collide with the component molecules of the gas sample; for example, air, *i. e.*, nitrogen, N_2, oxygen, O_2, carbon dioxide, CO_2, with added ammonia, NH_3, as odorant. One result of this collision between electrons and molecules is to strip off an electron from each of the gas molecules, or to "ionize" the gas molecules, to produce positively charged ions such as N_2^+, O_2^+, CO_2^+, NH_3^+.

The ions are in turn accelerated along a determined path by a series of plates which are maintained at a negative voltage by means of an external battery. These plates are provided with fine slits. Many of the positively charged ions are attracted to the negatively charged plates and hit these. A few of the ions, however, get through the fine slits and proceed down the mass spectrometer tube until they enter a region set between the poles of an electromagnet. There, the ions are deviated from their previous linear motion into a circular path by the magnetic field in a particular fashion such that the radius of the circular path differs for ions of differing mass. Thus, the magnetic field "analyzer" separates the mixture of ions on a basis of mass, the ions of N_2^+ (mass 28) traveling in a circular path of different radius from the ion O_2^+ (mass 32).

When the ions leave the magnetic field, they are passed through a fine collimating slit in the back of which is a collector plate. Since the paths of different types of ions are now different, it can be arranged for only one mass species (say N_2^+) to pass through this last slit and to reach the collector plate.

By changing either, or both, the accelerating voltage or/and the magnet current, it is possible to direct ions of desired mass through the final slit onto the collector. Thus, one would set the accelerating voltage to focus NH_3^+ (mass 17) on the collector and measure the number of such NH_3^+ ions reaching the collector. This number, which is proportional to the concentration of NH_3 in the gas sample, is read from an appropriate amplifying meter connected to the collector. Then, the accelerating voltage is set to focus N_2^+ (28), O_2^+ (32) and CO_2^+ (44) successively on the collector and the meter read for each of these. In this manner, the ratios and absolute concentrations of the various constituents of the gas may be determined. This method will also serve for complex mixtures of all sorts of compounds, provided proper calibrating procedures are used.

One particularly worth-while feature of the mass spectrometer is its ability to analyze for isotopes of a given element. It should, therefore, be possible in the field of odor research to label or "tag" a compound with a small amount of an isotope in its makeup, for example $N^{15}H_3$ in the NH_3 of the above case and to analyze the final gas mixture for $N^{15}H_3$ (mass 18) as well as the common $N^{14}H_3$ (mass 17). Furthermore, if the odorous compound is present in appropriate concentration, it should be possible to determine if the odorous compound (ammonia in this case) is absorbed on the nasal surface of the subject by analyzing sufficiently large samples of such epithelial surface for traces of N^{15} by means of the mass spectrometer.

It is conceivable that one may follow the path of an isotope into the body of the subject by using a technique even more sensitive than the mass spectrometer. "Tracer" experiments could be devised which would make use of radioactive rather than stable isotopes. It is possible to synthesize some of the organic compounds (possessing odor) with radioactive carbon and to trace the course of such radioactive substances through the environment onto the sensitive "detector" or nasal surface and into the body of the host.

This method is, to be sure, limited to "safe" radioactive materials. The sensitive detectors available, however, make it possible in certain cases to work with extremely low concentrations of relatively safe radioactive compounds and to get reproducible and accurate results.

Another class of versatile instruments are the optical spectrometers, which can determine the *absorption* of selected wavelength bands of light by a gas sample. Instruments are available for study of the ultraviolet, visible, and infrared regions of the spectrum. In general, these instruments are by no means as sensitive as the mass spectrometer or radioactive indicator methods, particularly when dealing with gas samples.

In principle, a given compound has a specific "color" or will absorb specific wavelengths of light depending upon the composition of the substance and its chemical structure. However, the extent of the absorption of light (which is the property experimentally measured) is a function of the concentration. Since the latter is low for most samples of interest here, the accuracy becomes correspondingly low although some compensation can be achieved by using long sample tubes with resultant long light path for measurement of absorption of the selected light.

In certain specific instances, high sensitivity may be obtained by such optical methods. For example, traces of mercury in air may be determined by illuminating a sample with a mercury arc lamp and photoelectrically determining the extent of "resonance absorption" by the mercury vapor in the sample. Traces of carbon dioxide may be detected in air by using an infrared source with a special filter consisting of a sample of carbon dioxide of known pressure and a thermocouple or other variety of infrared detector.

The "emission" type of optical spectrometer, wherein the sample is subjected to a high energy source such as an arc, spark, or flame to cause *emission* of a spectrum which is characteristic of the substance under investigation, may find use in this field. A recent development in this group is the flame photometer. Here, the air sample is introduced directly into the flame. If the air contains sodium in any form, a yellow flame results; potassium, a red flame; *etc.* Under controlled flame conditions, the intensity of the color is quantitatively related to the concentration of the element. By means of the flame photometer, parts per million of sodium and potassium in air are rapidly and accurately determinable.

Still another line of approach to trace analysis is through the use of various absorption reagents whose reactions may be converted into indicating and recording instruments. There are many such devices already in existence, and many others can be foreseen. The basic principle used in such devices is to draw a sample of gas, at known rate, through some reagent whose color, or electrical conductivity, or turbidity (or other physical-chemical property) is changed by reaction with the component of interest. The color change can then be translated into a photoelectric meter reading, the conductivity change into an electrical bridge meter reading, *etc.* By collecting continuous samples over a sufficient and known time interval to accumulate enough color change, or conductivity change, *etc.*, to give appreciable readings, it is possible to determine very slight traces of specific substances in a gaseous system. The absorbant need not be a liquid. It may be a paper tape impregnated with the reagent, the color change of which is determined by a photocell.

The last few years have witnessed the introduction of sensitive turbidity and light-scattering instruments for determination of concentration and particle size of aerosols, smokes, mists, *etc.* In these devices, the intensity of the light scattered by the particles is determined at various selected angles and used in calculating the physical properties mentioned above.

The second component in the odor system, namely the detector or sensing element, offers an interesting challenge since it cuts across many disciplines. From our point of view, it seems that controlled physical experiments can be performed to ascertain some of its characteristics.

Like any other detector, its sensitivity, reproducibility, fatigue characteristics, selectivity, range, threshold, and overload points should be determinable. Many of these characteristics could be approached through accurate control of the environment. For example, the combined use of radioactive tracer compounds and a radioactivity detector on the nasal surface should enable one to study and perhaps correlate the instantaneous concentration of radioactive odor substance in the nose and the "smell" reported by the subject. The interposition of selective infrared filters should permit a definitive answer to the notion that infrared radiations from some odorous substance rather than the physical contact of the substance constitute the odor stimulus on the nasal surface. The effect of introducing activating or inactivating substances, such as enzyme inhibitors, on the sensitive odor-detecting surface should yield considerable information concerning the sensing element, at least in a qualitative way.

A chemical study of the compounds present in the sensitive area should now be possible through use of such delicate fractionating techniques as paper chromatography and paper electrophoresis. Such methods are successfully employed in related biological problems and should be directly applicable here. The use of radioactive tracers should permit accurate study of diffusion through the sensing element and of the changes in surface properties when odor stimulants are present.

Especially when the subjective "smell" reactions of the subject are related to the objectively measured nerve responses, will progress be possible toward an instrument for odor measurement. In the past few years, there have been very significant developments in the instruments for stimulating and measuring the response of nerves to various stimuli. It would seem that these methods are directly applicable to a study of the converter-recorder or odor-nerve response system. The stimuli here are odors. If produced by actual physical interaction between the odor substance and the nerve endings or sensing element, then the analogy with the response of nerves involved in other physiological activity is certainly direct and the methods of study can be analogous.

Do the odor sensing nerves behave electrically like other nerves toward corresponding stimuli? If they do, excellent electrical stimulators and electrodes are available from the field of neurophysiology, and sensitive and stable amplifiers with a wide range of electrical characteristics are also available for detailed studies. Application of these instruments should lead to some interesting and directly useful results.

If it should be established that odor substances generate electrical impulses in the odor-sensitive nerves, one could by-pass the subjective response of the individual and measure such electrical responses directly. Furthermore, if the frequency of the nerve response were related to the concentration of the odor substance, or if the pattern of response were related to the structure of the odor molecule, it might be possible to set up an objective measurement of odor response, *i.e.,* an experimental odor scale.

In any case, whether or not the particular correlations suggested above are found, it is important to realize that these techniques are available, are in use in other fields, and should be tested here with the view of setting up experimental criteria for evaluating theories and for securing new results. Such a course should promote progress in the field of odor research.

PROBLEMS IN ODOR RESEARCH FROM THE VIEWPOINT OF THE CHEMIST

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Introduction

The celebrated British physiologist, Adrian,[1] said in a lecture on the sense of smell, given in 1947, "We know so little about the sense of smell that I must start by excusing myself for choosing such an unusual subject for a lecture. My only excuse is that it is unusual. I am sorry to say that I have not much to add to the little that is known. . . ." Later he mentions how easy it is to make an artificial eye (the camera) or an artificial ear (the microphone) and how difficult it would be for chemists to make an artificial nose. Let me remark here that an attack in this direction, namely an attempt to construct an artificial nose, might lead to important discoveries about olfaction. Then again, think how valuable an artificial nose would be to tell you when you have halitosis.

In the *American Scientist* for April 1953 Griffin[2] says, "The sense of olfaction still taunts the physiologist with his lack of knowledge of even its most basic aspects." Then Doctor Amos Turk asked me to present this paper about the relationship between enzymes and odor. I had not been aware that there was any particular relationship between enzymes and the perception of odor. A review of the references on odor, kindly sent to me by Doctor Dean Foster, however, has revealed the existence of several which refer to enzymic theories of olfaction.

Enzyme Theories

In 1937 Jerome Alexander[3] proposed that odor-producing substances affect the catalyst balance of the olfactory cells (a) by modifying the existing catalysts; (b) by forming new catalysts; or (c) by inhibiting all or a part of the activity of normal cellular catalysts. More recently Kistiakowsky[4] has proposed a similar theory of odor perception. Here the chemical reactions are:

$$\begin{array}{ll} A \rightarrow A^1 & A^1 \rightarrow A^{11} \\ B \rightarrow B^1 & B^1 \rightarrow B^{11} \end{array}$$

and so on. Each of these chemical reactions is catalyzed by some enzyme. The compound having odor inhibits one or more of these enzymes, altering the concentration of A^1, A^{11}, B^1, B^{11}, *etc.* These changes in concentration cause signals to be given to specific nerves and these nerves send messages to the brain. From what I know about the inhibition of enzymes, it appears most unlikely that the mechanism proposed by Kistiakowsky is correct. There exist a few rather specific inhibitors of enzymes although there are a great many inhibitors which affect enzymes generally. Moreover, generally speaking, the substances that we smell, and in the concentrations needed for us to smell them, would not be likely to have any effect whatsoever upon any enzymes now known to exist. In order for this theory to be plausible it would be necessary to have an array of enzymes with new and unusual properties in the epithelium of the nasal cleft. Finally, even if an odorous substance should inactivate some enzyme and thereby cause a change in the concentration of some substance, we have yet to explain how this change in concentration could stimulate the olfactory nerves.

El-Baradi and Bourne[5] have found that alkaline phosphatase is present in the olfactory mucosa as well as in the taste buds of the tongue, as shown by the Gomori test. They have observed that vanillin inhibits this alkaline phosphatase. So they have advocated a theory of taste and odor akin to that of Kistiakowsky. Now the enzyme, alkaline phosphatase, is present, widely distributed, in the animal body and its inhibition by vanillin is not at all surprising. I can see no reason to connect either the presence of this enzyme in the nasal epithelium or its inhibition with the mechanism of smell.

We know of many chemicals which inactivate enzymes, but some of the best inactivators are odorless substances, such as monoiodacetate, sodium fluoride, mercuric salts, silver salts, and copper salts. As I have already stated, inactivators of enzymes usually are relatively unspecific in their action and inactivate not just one enzyme, but a large number of enzymes.

What does the biochemist know about the biochemistry of odor perception? He knows very little, it is true, but he does know that sensation requires living cells which must have nourishment in the form of carbohydrates, amino acids, lipids, vitamins, inorganic ions, oxygen, and water. He knows that certain hormones may possibly play some role. He knows that practically every life process requires a source of immediate energy in the form of ATP, or adenosine triphosphate. He knows that all or nearly all of the chemical reactions which occur in living things are catalyzed by a multitude of enzymes acting in an orderly manner.

Now enzymes are undoubtedly necessary for hearing, seeing, tasting, smelling, touch-pressure, hot, cold, and for the sense of pain. This, however, does not mean that any enzyme is involved in the primary mechanism whereby nerve endings are stimulated. In recent years Wald[6] has performed an excellent piece of work in explaining how rhodopsin, otherwise known as visual purple and present in the retina of the eye, is broken down by light into retinene and protein and then is reduced by the action of an enzyme, called retinene reductase, to form protein and vitamin A. Later the protein and vitamin A are converted into rhodopsin again. It appears likely that the retinene produced from rhodopsin, stimulates the optic nerve to send messages to the brain, these being interpreted as vision. The fovea in the retina does not contain rhodopsin, but probably does contain a similar substance which is decomposed by light rays. This work of Wald marks a beginning and is of great value, but it must be regarded as preliminary.

Radiation Theories

The mechanism by which odorous substances are able to stimulate the olfactory receptors has been said to be caused by the production of infrared waves by odorous substances. One variation of the radiation theory, that of Beck and Miles,[7] assumes that the epithelium of the nasal cleft itself gives off infrared radiations and that the odorous substances absorb these radiations in a manner specific for each basic odor and that the cooling effect thus produced results in a stimulation of the receptors. Physicists have dragged in many of the known concepts of modern physics, such as Planck's constant, the Boltzman constant, and the Raman effect.

I am not a physicist; nevertheless I am willing to classify these radiation theories as unconvincing and even preposterous. Of the various research articles about odor perception that I have read, the one which has done the most in my opinion to overthrow radiation theories is that written by Young, Pletcher, and Wright.[8] These workers point out that the deuteroxyl counterpart of N-butyl alcohol has exactly the same odor as the original N-butyl alcohol, although its infrared spectrum is different. They note, on the other hand, that certain D and L compounds differ in smell,[9] although here the infrared spectra are identical.

The Source of Energy

What is the source of energy required to stimulate the receptors of smell?

E. L. Goldwasser[10] wrote in 1947-48, regarding the production of energy needed to stimulate olfactory receptors, that it may come from "Pauling's electro-chemical energy source deriving from the modification of atomic bonding angles within a molecule at the time that the molecule goes into solution." From what I know about living cells I doubt that this is true.

We have learned in recent years that the primary source of energy for muscular contraction, glandular secretion, and various other physiological processes is produced by the breakdown of adenosine triphosphate. It would appear likely that the energy consumed in the process of smelling, tasting, hearing, feeling, and seeing also comes from this adenosine triphosphate, or ATP. If ATP can decompose rapidly enough to enable the hummingbird's wings to contract too fast to be seen, or the canary bird's heart to contract 1000 times per minute, then this breakdown should be rapid enough for the functioning of the receptors for various sensations.

Comments on Statements

Moncrieff [11] says in his book that lecithin is a protein. This is an error. He says that carbon monoxide is odorless. J. B. S. Haldane states that carbon monoxide has odor if one smells it in sufficient concentrations. Moncrieff claims that hydrocyanic acid, benzaldehyde, and nitrobenzene all smell alike. They smell different to me. He mentions 30 elements which, under atmospheric pressure and ordinary temperature, have no odor. I find that the alloy, brass, has a marked odor. Moncrieff claims that palmitic and steric acids are without odor. I find this to be untrue. He states that cases of preferential anosmia are not well established. All I wish to say is that, if such cases are not well established, then they should be fully investigated.

The claim that albinos are anosmic has been denied by Foster.[12] Moncrieff [11] supports the influence of pigment on the ability to smell by noting that black pigs will not eat the poisonous *Lachantes tinctoria,* while white pigs will; and that in the Tarentino only black sheep are raised, since the white ones are poisoned by *Hypericum cristum.* These statements, by themselves, mean little or nothing. Nevertheless the possible effect of color on odor sense should be tested out completely and thoroughly.

Goldwasser [10] has claimed that chemical theories have failed to explain the odors of saturated paraffins. Now saturated paraffins are admittedly not so odorous or so reactive as unsaturated paraffins, but they can exert chemical forces, such as van der Waals' forces. Besides, saturated paraffins might dissolve in the fatty substances of the nasal epithelium and cause a stimulation by the physical effect of their mere presence.

One of the best of the research papers that I have read on odor is the one by Adrian[1] already referred to, who describes how he detected the transmission of nerve impulses from the nose of an anesthetized animal to the olfactory bulb in the brain. By placing an electrode in the olfactory bulb of a rabbit Adrian has observed that a nervous discharge occurs at each breath. When smell is strong, the nervous discharge is increased. Adrian found the rabbit nose to react well to fruity and aromatic smells while the nose of the cat reacted well to foul smells but not to the odor of vegetables or grass. Let me note that Adrian has advanced no theory of odor.

What Can Be Done by the Biochemist?

Enzyme poisons in high dilution can be sprayed into the nose to ascertain how they interfere with smell. By enzyme poisons I mean substances like eserine, prostigmine, atropine, tri-o-cresyl phosphate, sodium fluoride, iodacetic acid, *etc.* As an example, formaldehyde paralyzes the sense of smell.

The biochemist can isolate the mucous membrane of the nasal cleft and can find out what enzymes are present. He may discover new enzymes. He can find out how those enzymes are effected by chemical compounds, both odorous and without odor.

Average threshold values for a great many chemical compounds should be accurately established. At the present time there is a considerable lack of agreement.

Much more research should be carried out using odorous compounds and comparing these with compounds where the deuterium has replaced some of the hydrogen. More research should be carried out using D and L isomers as well as meso compounds also.

The biochemistry of the brain and nerves has been considerably neglected as compared with that of liver, muscle, and other tissues. The biochemist should investigate not only the enzymes of brain tissue, but also the metabolism of the brain.

The olfactory epithelium is stated to be yellowish-brown in color and to be most deeply colored in those animals in which olfaction is most sensitive. What is this yellowish-brown pigment, I may ask, and has it any connection with the perception of odor? Is this pigment bleached by odorous substances in a manner analogous to the bleaching of rhodopsin by light? I should like to point to the possibility that this yellow-brown pigment may be decomposed by odorous substances resulting in the sensation of odor. Its destruction might cause odor fatigue.

A Theory of Olfaction

Freely admitting that far too little is known about the olfactory process to permit one to construct a complete theory, nevertheless, against my better judgment I am going to propose the following admittedly sketchy and incomplete scheme:

Chemical No. I reacts with receptor A and displaces molecules from A.

These displaced molecules stimulate the nerve to send an impulse to the brain.

Chemical No. II reacts with receptor B and displaces molecules of B. Chemical No. III reacts with receptor C and displaces molecules of C, and so on.

Large amounts of these chemicals displace more molecules than do small amounts of these chemicals.

Chemical No. I reacts most readily with receptor A, but also reacts to a slight extent with receptor B and with receptor C.

When chemical No. I has displaced molecules of receptor A there is a dearth of these molecules available and fatigue results until the supply can be replenished.

Some individuals possess a greater number of receptors A than of receptors B, or C, or *vice versa*. This would explain preferential anosmia.

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Part II. The Olfactory Process, Status of Present Knowledge

THE ODORANTS

By R. W. Moncrieff
Girvan, Ayrshire, Scotland

Smell is a primitive sense; it emerged long before vision. Even the simplest of animals such as the protozoa and coelenterates have some sort of chemical sensibility. As the scale of animal life rises, this chemical sensibility differentiates into a common chemical sense, into taste, and into smell.

Smell served primitive needs, notably those of nutrition and of reproduction. If these two needs are served, the race will survive; if they are not, it will die. The sense of smell guides animals to their food and to their mates; it has made possible the growth and the survival of animal life in the world. The coming of civilization has lessened man's dependence on his nose. Land is farmed and animals are bred and butchered as required. Food supplies, although still constituting a problem in some parts of the world, are a matter for community organization rather than for individual hunting. As the sense of smell has been used less and less, so its delicacy has deteriorated, and the keenness of perception amongst humans today is doubtless but a shadow of what it once was. Nevertheless, at the zenith of its powers, smell made such a powerful impression on the central nervous system of our ancestors that it can still surprise us by flashes of its former power. Particularly does this apply to our early experiences. Probably all of us know of some smell, perceived however inattentively, which instantly reminds us—and usually very vividly—of a childhood scene.

Amongst the animals, keenness of smell still persists and most mammals have very much more sensitive noses than we have, although changes of environment can reduce its efficacy. Hounds today are slower to follow the scent of a fox over ploughed land than they were twenty years ago, and this is attributed to the fouling of the land by oil from the tractors with which it is worked; the smell of the oil presumably obliterates that of the fox. A trace of formaldehyde incorporated in a meat jelly will not be perceptible to us, but a cat will decline to eat it. Quite evidently the cat can smell the formaldehyde sufficiently well to object to it, even though the odor is too faint for us to detect.

Odorant materials come from many sources, some of them from the animal kingdom. Most land animals themselves have an odor; the ewe recognizes its own lamb by sniffing at it and, if the shepherd loses a lamb, he will skin it and tie the skin round an orphan lamb so that the ewe whose lamb has died will accept the orphan. Animal odors reach their highest intensity in the sex attractants which are carried by the male musk deer and by both sexes of the civet cat. The odor of humans, particularly of their perspiration, has been described by Barail.[1] It largely depends on the nature of the food that is eaten.

The vegetable kingdom supplies a much greater variety of odors from the roots, stems, leaves, and flowers of plants. Those flowers that smell pleasantly attract the most attention, but it is only the minority of flowers that are pleasantly odorous. Müller,[2] who examined 1266 different kinds of blossom, found that only 174 had odors that could be described as floral; odors like heliotrope, honey, jasmin, or orange blossoms; while 211 had cabbagelike odors; and more than half of them all were inodorous. Müller also examined 738 different kinds of leaves and found that about half of them were characterized by the fresh "green" odor of α, β-hexylene aldehyde, a compound which is also partly responsible for the flavor of the tea we drink. The odors of natural products are due, as a rule, to the presence of very small quantities of some powerfully odorant material. The chemist has been able to extract these odorant principles and to determine their chemical constitution and thereafter to synthesize them. Usually the perfumes of fragrant flowers are complex and are due, not to one odorant chemical constituent, but to the combined effect of many. There are perhaps thirty different chemical odorants contributing to the perfume of the rose, and it is consequently no easy matter to match its perfume exactly by making mixtures of synthetic chemicals. Comparison of the natural rose otto with a synthetic rose perfume usually reveals a big difference. Occasionally one individual chemical odorant is almost entirely responsible for a flower perfume; *e.g.*, methyl anthranilate is much the most important contributor to orange blossom perfume.

Natural odors are more or less limited in number and our olfactory equipment has evolved along lines which have enabled it to recognize and to distinguish these odors. The industrial development of the last 100 years or so has brought odors new to man, odors that had not previously been smelt at all, odors such as those of coal gas, acetylene, steam trains in tunnels, cigarette smoke, and so on. The modern tendency to condition air and to re-circulate it has brought with it problems of purification and particularly of odor removal. The conditioned air supplied to some railway sleepers is often tainted with tobacco smoke. Within the last thirty years the synthetic chemist has produced many thousands of new odorous compounds and our olfactory apparatus has coped surprisingly well with this influx of new material. Some of the synthetics such as hydrogen sulphide and its alkyl analogues, the mercaptans, have repulsive odors, but many others have odors that are highly esteemed. Long chain fatty aldehydes, *e.g.*, lauryl aldehyde, have been used in considerable quantities in perfumery; and without their use the highly sophisticated note that characterizes the modern perfume would be unobtainable. Some of the synthetic macrocyclic lactones, ketones, and esters have contributed valuable musk- and civet-like odors.

But it is one thing to synthesize a chemical with a new odor and quite another to know why it has it. Why should some substances be odorous and others not? This is one of the many questions connected with odor that have never been completely answered. But we can go some distance toward an answer.

It is generally accepted that, for a substance to be odorous, it must be at least slightly volatile so that particles, or perhaps molecules of it, can be swept by air currents into the nostrils and thence inspired into the olfactory cleft. The way in which odor always travels down-wind lends support to this view. Actual contact of material particles with the nasal apparatus is necessary for odor to be sensed. Substances such as iron, glass, and stone, which have no appreciable vapor pressure, are invariably inodorous. No substance which is not continually losing molecules to the air can be odorous. Nor can even the most powerful odorants be smelt if they are totally enclosed, as in a glass phial. Sound and light can pass through air-tight barriers, but smell cannot. The very way in which we sniff to inspire more air higher up the nose shows, surely, that the stimulus for odor is in the air; the molecules of the volatile odorous substances constitute the stimulus.

The second requirement for a substance to be odorant is that it shall be capable of solution in the fatty parts of the olfactory apparatus. Most of the substances that are strongly odorous are fat-soluble, *e.g.,* chloroform, methylene chloride, benzene, and the alcohols. Those substances, such as salt and sugar, that will dissolve in water but will not dissolve in fatty materials are never odorous. Solubility in water is a necessary criterion for taste but may not be necessary for odor. Certainly some of the powerful odorants are only very slightly soluble in water. Naphthalene, for example, is only soluble to the extent of 1 part in 30,000 parts water. It may well be that a substance which is reasonably soluble in both water and lipoids is most likely to have a strong odor. As Backman[3] has pointed out, the middle members of a homologous series possess both water and lipoid solubility and are the most strongly odorous. Butyl alcohol, for example, has a much more powerful odor than methyl and ethyl alcohols which have good water solubility but poor lipoid solubility, and a more powerful one, too, than decyl or cetyl alcohols which have good lipoid solubility but which are substantially insoluble in water.

Thus we have two criteria for a substance to be odorous. Firstly, it must be volatile; secondly, it must be soluble in the tissues of the olfactory region. This certainly requires fat solubility and is enhanced by slight water solubility. That odorant principles are both volatile and fat-soluble can be illustrated by a piece of butter which has been kept in the same refrigerator as some herring; part of the odorous principles from the herring have volatilized, dissolved in the butter, and conferred on it an objectionable fishy taint. If the odorant principles had not been both volatile and fat-soluble, the herring taint could not have appeared in the butter.

There are, however, many substances that are both volatile and fat-soluble but which are, nevertheless, inodorous. Glycol and glycerol are examples. Some other requirement must be met. Some workers notably Ogle,[4] Fabre,[5] Heyninx,[6] Teudt,[7] Zwaardemaker,[8] Krisch,[9] Dyson,[10] and Beck and Miles[11] have believed that this third requirement consists of some form of inter- or intramolecular vibration. There may be some evidence that insects are affected by vibrations from odorant materials, but there is none, so far as I know, that suggests that olfaction in mammals is due to molecular vibrations of the odorant. Dyson[10] made out a case for a correlation between odor and absorption in the Raman spectra which at the time attracted great interest. In retrospect, however, it seems unconvincing and I am inclined to agree with Naves,[12] the eminent Swiss chemist, who recently wrote, "I cannot bring myself to find any reason whatever in this theory that odor is connected with vibrations in the molecule or of the molecule . . . (it is) absolutely without experimental foundation."

Another approach to the problem has been based on the well-known parallelism between chemical reactivity and odor. Those substances which are chemically reactive often have strong odors; in particular chemical unsaturation is almost always accompanied by intense reactivity and strong odorant properties. Thus, ethane, which is chemically saturated, is almost odorless; ethylene, which has a double bond in its constitution, has a rather faint sweetish smell; and acetylene, which has a triple bond and is, so to speak, twice unsaturated, has a strong garlicky odor. The saturated aldehydes, although they have fairly strong odors, do not compare in intensity of odor with those unsaturated aldehydes such as acrolein. So marked is this parallelism between odor and unsaturation that several workers, notably Woker[13] as early as 1906, Marchand,[14] Durrans,[15] and Delange,[16] have ascribed odor mainly or in part to chemical unsaturation, including such groups as carbonyl $C=O$ in this category. Certainly, unsaturation or residual affinity, or what else it may be called, often runs parallel with the appearance and intensity of odor, but it has always been perfectly clear that unsaturation *per se* could not be the primary cause of odor, because those paraffins such as hexane, heptane, and octane, although as completely saturated in the chemical sense as it is possible for a substance to be, have in fact quite strong odors.

If a study is made of the relation between chemical constitution and odor, so many trends and similarities can be seen that it seems certain that a close correlation would be found if only the pattern could be clearly seen. Perhaps three examples of apparent uniformity will illustrate this statement.

(1) One of these is the olfactory behavior of the elements in the elementary state. There are only seven elements that are odorous out of nearly 100 known; these are fluorine, chlorine, bromine, iodine, oxygen (as ozone), phosphorus, and arsenic. If the elements are arranged in a series according to the potential difference between the element and a solution of its salt, in such a way that the greater this potential difference, the higher would be the position of the element, then we have what is known as the Electrochemical Series. A more highly placed metal will displace a lower metal from its salts, *e.g.*, zinc or iron will deposit copper from a copper sulphate solution. The series is no arbitrary arrangement, but has a well recognized significance. Such a series of the more common elements is shown on page 77.

It is at once obvious that six of the seven odorous elements occupy six of the last seven places in the table. Evidently an electronegative or non-

METALS

These metals liberate hydrogen from acids

Cesium
Rubidium
Potassium
Sodium
Lithium
Barium
Strontium
Calcium
Magnesium
Aluminum
Chromium
Manganese
Zinc
Cadmium
Iron
Cobalt
Nickel
Tin
Lead

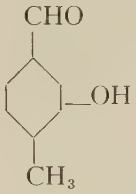
Hydrogen
Antimony
Bismuth
Arsenic
Copper
Mercury
Silver
Palladium
Platinum
Gold
Iridium
Rhodium
Osmium

NON-METALS

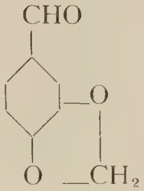
Silicon
Carbon
Boron
Nitrogen
Selenium
Phosphorus
Sulfur
Iodine
Bromine
Chlorine
Oxygen
Fluorine

metallic character is closely associated with odor. It is worthy of note, too, that sulfur and selenium, whose compounds are often repulsive, occupy very low places in the table. Surely there is more than coincidence in this.

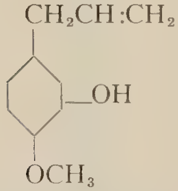
(2) Another of these promising observations is that the 1:3:4 arrangement of substitution in the benzene ring usually leads to a pleasant odor. The odors of vanilla, heliotrope, and cloves are due respectively to their content of vanillin,



piperonal or heliotropin,

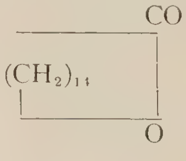


and eugenol,

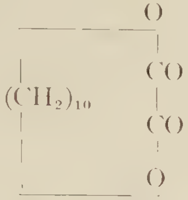


in all of which the benzene ring is substituted in positions 1, 3, and 4. Such uniformity is at least suggestive of a close relationship between constitution and odor.

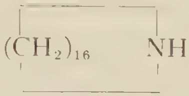
(3) A third relation which perhaps looks even more promising is that between the number of atoms in the ring of macrocyclic compounds and the odor. Hill and Carothers[17] synthesized a number of macrocyclic ketones, lactones, and esters. They showed that, if there were 13 atoms in the ring, a cedar-like odor was evident; if there were 14, 15, or 16 atoms in the ring, musky odors prevailed; and if there were 17 or 18 ring atoms, the odor was civet-like. Such compounds as pentadecanolide



and decamethylene oxalate



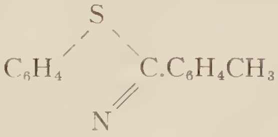
both had musky odors. So, as was shown by Ruzicka, Salomon, and Meyer[18] had hexamethylene imine:



It is clear that, within wide limits, the identity of the reactive groups in these macrocyclic rings is unimportant; what does matter is the size of the ring, the number of atoms in the ring. There could hardly be more direct evidence of the dependence of odor on chemical constitution, and, indeed, the three examples given could be increased in number to twenty or more without difficulty.

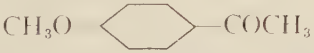
Despite this promise, the relation between chemical constitution and odor is by no means straightforward. There are many inconsistencies and anomalies. We might in turn consider three of these, *viz.:*

(1) The presence of a sulfur atom in the molecule usually leads to a strong and unpleasant odor as in the mercaptans and as in oil of garlic; but if the sulfur atom is included as a member of a ring, its influence on the odor may be quite beneficent. Bogert and Stull[19] showed that 2-tolyl benzothiazole

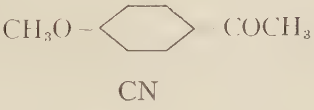


smelt of tea-roses and so did several similar compounds.

(2) The 1:3:4 substitution of the benzene ring does not invariably give substances with pleasant odors. Bogert and Curtin[20] showed that even although *p*-methoxyacetophenone



had a floral odor, yet when this was further substituted to give 3-cyano-4-methoxyacetophenone



this product was nearly odorless.

(3) The effect of the position of substitution is often very great; compounds that are very similar isomers of each other may have very different odors. Typical instances are the methyl esters of *o*- and *p*-hydroxybenzoic acids, the characteristic wintergreen odor of the former is quite missing in the *para* compound. Other pairs which show considerable differences are: α- and β-ionones; eugenol and iso-eugenol.

There are, therefore, very considerable difficulties in the way of any straightforward correlation of odor with chemical constitution. Perhaps the greatest difficulty is to be found in the stereoisomers. These are substances which are almost identical in chemical properties and which possess the same groups, but which have some inequality of spatial arrangement of the groups. Thus geraniol and nerol have perceptibly different odors, as have iso-α-irone (*trans*-2,6-methyl-6α-ionone) and neo-irone (*cis*-2,6-methyl-6α-ionone). Even optical stereoisomers with different odors have been reported. If, therefore, two substances which are made up of molecules that are mirror-images of each other can have different odors, it is evident that molecular shape has a good deal to do with odor. It is now widely recognized that molecular shape determines many physiological characteristics. Only the γ-isomer of benzene hexachloride is a powerful insecticide; only the *dextro* form of ascorbic acid is a powerful vitamin.

Let us therefore postulate that, in order to be odorous, a substance must not only be volatile and soluble in the nasal tissues, but must also have a molecule of suitable shape and dimensions, such molecules being complementary in shape to molecules that abound in the olfactory receptors. If we do this, most of our difficulties disappear, and the idea is not dissimilar from Pasteur's explanation of the different behavior of optical isomers by supposing that the nerve and tissue substances are themselves asymmetric and therefore react differently toward the right-handed and left-handed isomerides.

If we postulate that odor is due to a combination of volatility, lipoid solubility, and molecular shape, it is possible to account satisfactorily for most of the observed olfactory phenomena. For example:

(1) Some substances are odorous; some are not. If the substance is volatile and has a suitable molecular shape, it will be odorous; otherwise it will not. Probably we can leave lipoid-solubility out at this stage because it also is determined by molecular shape.

(2) There are many different qualities of odor, each due, we believe, to a geometrical image thrown onto the cortex of the brain. There may be half a dozen different kinds of receptor in the olfactory area; the particular combination of these that are stimulated together with the intensity of stimulation determines the pattern that will be projected onto the cortex. Adrian[21] has, for example, shown that in a rabbit's nose an *oily* smell activates the *back* of the olfactory region whereas an *ester* smell activates the *sides* as well. As Adrian wrote, "In the rabbit, the inspection of records of the olfactory discharge from different regions will show whether the smell was fruity or oily." Evidently there are different kinds of receptors and it

is not difficult to believe that molecules of a particular shape could find a suitable lodgment on one kind of receptor but not on another.

(3) The nature of an odor will sometimes change on dilution. Civet is repulsive in the concentrated form but attractive when diluted. This is easy to understand if we postulate that there are two kinds of receptors that the civet molecules normally occupy. The molecules will probably have a preferential affinity for one of them, and if there are only relatively few molecules present, *i.e.*, if the civet is dilute, only one kind of receptor is occupied; but if the molecules are very numerous, *i.e.*, if the civet is concentrated, then both kinds of receptor will be occupied. According as to whether one or two kinds of receptor are occupied, the smell will be different.

(4) The onset of olfactory fatigue on continued smelling is due to all the receptor sites becoming occupied by odorant molecules. No new sites are available, so no new energy changes can take place on the receptor systems until the molecules already there have been absorbed by the tissues.

(5) Some odors are neutralized. For example, the odor of a blood hydrolysate is objectionable, but in the presence of some other odorants hardly any of the original odor can be observed. It is conceived that if two odorous substances neutralize each other, *i.e.*, individually each is odorous but together they are inodorous, this is because the molecules have an attraction for each other. Sites which would hold either type of molecule cannot hold two together.

(6) Some animals are much more sensitive to smell than is man. This is due to their greater wealth of olfactory sites on which the odorous molecules can lodge.

(7) Stereoisomers, even optical stereoisomers may have different odors. Clearly left and right-handed molecules cannot always be expected to fit into the same sites.

(8) Slight differences in orientation, *e.g.*, between α- and β-methyl naphthyl ketones, may cause considerable changes in odor. Clearly such changes, involving changed shape of the molecules, may well alter the suitability of the molecules for filling available receptor sites.

(9) Substances of different chemical constitution may have similar odors. The explanation is that they are, in some respects, similar in configuration and can occupy the same sites. Most substances that include a tertiary carbon atom in their constitution have a camphoraceous odor.

(10) Unsaturated substances are often strongly odorous. The reason is that unsaturation renders the molecule more flexible, it imparts a strain to the molecule, and sometimes it encourages resonance. The greater the number of molecular shapes in which a substance exists, the more likely it is to find a suitable receptor site that will accommodate it. Furthermore, unsaturated substances readily form addition compounds and may well engage in some temporary form of chemical combination with the receptors themselves.

This theory is, therefore, that the only criteria that must be met for a substance to be odorous are: firstly, that it shall be volatile; secondly, that the shape of its molecules or of a part of its molecules must be complementary to that of some of the olfactory receptors. It appears to offer a reasonable explanation for the observed phenomena. In particular, it accounts for the undoubted tendency of chemical unsaturation to enhance odoriferousness, without precluding the possibility of saturated substances being odorous, as in fact they often are.

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THE OLFACTORY AREA AND THE OLFACTORY RECEPTOR PROCESS

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This paper is to acquaint those interested in the problems of olfaction with the olfactory area and its receptor mechanism. Since the olfactory area, however, is not a separate organ, but rather a specialized cell area of the upper respiratory epithelium, it is unwise to limit investigations of olfaction strictly to receptor end organs or anatomy as we do the eye or ear. The olfactory area of the upper nasal region of man is remote from the air streams produced during inhalation; and, because of this remoteness, an attempt will be made to show how the whole nasal area influences and possibly participates in the perception of odorants.

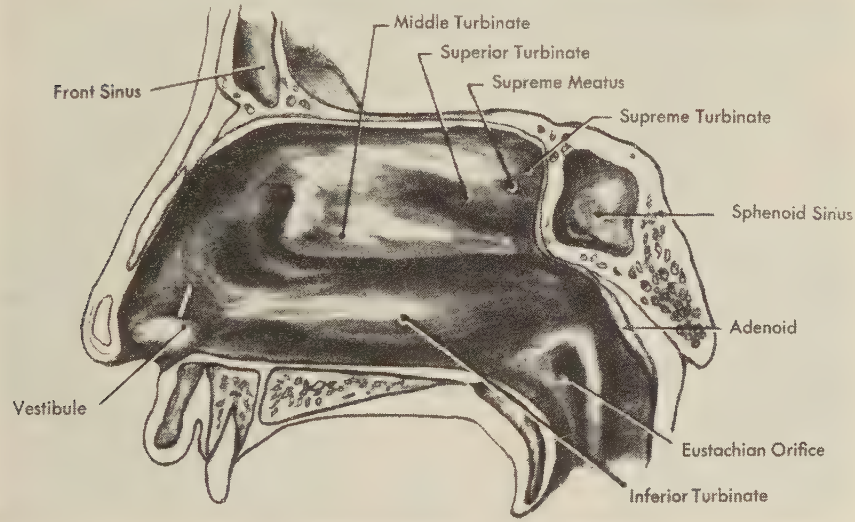


FIGURE 1. Lateral wall of nose showing turbinates.

The gustatory and olfactory senses have always been linked togther, but I shall attempt not to mention the sense of taste once. Rather, I shall attempt to point to the link that our sense of smell has to the combined sense modalities of warmness, coldness, pressure, and/or pain.

Primarily, I shall attempt to show that, since our inspired air must travel over such large and diverse surface areas of the nasal respiratory epithelium, we must conclude that the odorants in that air can act upon many types of end organs interspersed throughout that area as well as act singly on the olfactory end organs.

Therefore, to substantiate this thought, a rather short, but complete.

description of the nasal cavity will be given to illustrate the "variable duct system" through which our inspired air must travel before it reaches the pharynx. An attempt will be made to show that this whole nasal area is extremely prone to the sorption and retention of odorant particles and/or molecules before they actually reach the olfactory cleft to excite the sense of smell.

FIGURE 1 shows the nasal area, which is divided into a right and left cavity by the nasal septum. The anterior or forward opening is called the anterior nares, while posteriorly the cavity opens into the nasopharyngeal space. The whole area, right and left, is surrounded or supported by osseous, or bony, processes which are integral parts of the skull's osseous and cartilaginous formations. It is not necessary to consider these bone formations other than to say that bone and cartilage form the rigid construction frame for the nose's interior.

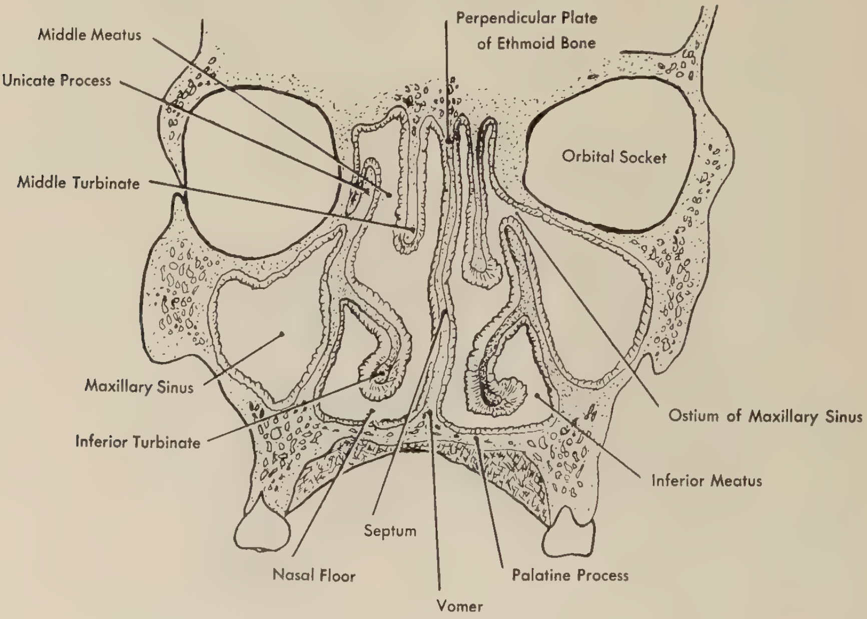


FIGURE 2. Schematic diagram showing coronal section of the head.

The floor of the nasal cavity (the inferior wall) runs obliquely backward and downward while the roof, or the superior wall, is angularly arched and is extremely narrow in most humans (1–3 mm). The roof, or superior wall of the nasal cavity, is the region where the specialized olfactory epithelium is found, and directly above this area, the cribriform plate of the ethmoidal bone occurs. The latter, or the bony cribriform plate with its attached epithelium, is the physical barrier between the brain and the nasal cavities.

The lateral walls of the nasal cavity, shown in FIGURE 2, are very irregular or convoluted. This irregularity is caused by the nasal turbinates (or conchae). The surfaces of the lateral walls possess openings to the sinus processes.

Each nasal concha or turbinate overhangs a meatus corresponding in length to the concha (shown in FIGURE 1). The meatuses are trough-like spaces, of varying depths, occurring laterally to each turbinal bone and thus follow the same nomenclature as the corresponding turbinate, *i. e.*, inferior, middle, superior, and supreme meatus.

The common meatus is that space intervening between the medial surfaces of the conchae and the septum of the nose and extending from the roof to the floor of the nasal cavity.

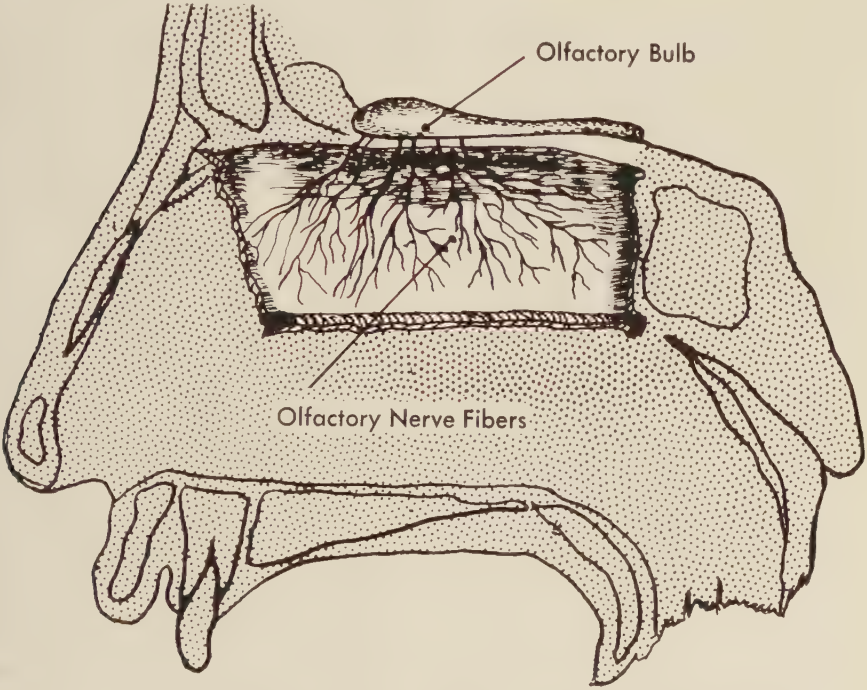


FIGURE 3. Cutaway schematic diagram of enervation of turbinate area.

The nasal vestibule is lined with a delicate continuation of the deeper parts of the outer skin. Those posterior to the vestibule are lined with mucous membrane which is continuous with the mucosa of the sinuses, nasopharynx, and eustachian tube. This mucous membrane may be divided into two major dissimilar portions: the respiratory and olfaction portions.

The *respiratory portion* principally covers the inferior turbinals, the lower half of the nasal chamber, the entire middle turbinate and corresponding areas of the septal mucous lining.[5,9,11]

The mucous membrane of the respiratory region is reddish. It consists, principally, of pseudo-stratified columnar epithelium containing ciliated cells and basal cells.[11] Secretions come from numerous branched alveolo-tubular glands which contain both mucous and serous cells. The mucous membrane varies greatly in thickness over the various regions.

The turbinates, or conchae, of the respiratory region are extremely vascular and possess a structure similar to that of erectile tissue; this is especially true of their outer ridges. The erectile tissue may be excited through reflex channels to cause considerable enlargement (engorgement) and swelling which may cause complete closure of the meatuses.[5,11]

The *olfactory portion* of the nasal mucous membrane (FIGURE 3) is limited to a relatively small area in the nasal cavity (±240 sq. mm). (Read reported the olfactory innervation to assume a 25 mm square pattern which would equal 625 sq. mm.[10,11]) It lines the surface of nearly all the superior turbinate, a very small part of the middle turbinate and the upper third of the nasal septum. The olfactory epithelium belongs to the pseudo-stratified columnar type, and unlike the respiratory portion, it has no distinct basement membrane or cilia. The olfactory portion consists essentially of three kinds of cells: (1) sustentacular or supporting cells; (2) basal cells; (3) olfactory cells.[5] McDowall has placed the thickness of the olfactory membrane at about 0.06 mm.[10]

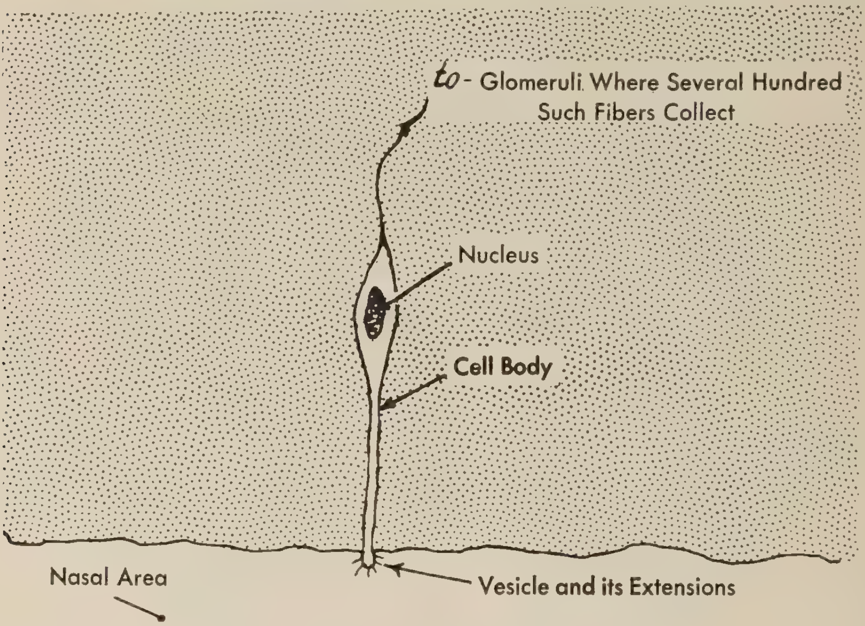

to - Glomeruli Where Several Hundred Such Fibers Collect
Nucleus
Cell Body
Nasal Area
Vesicle and its Extensions

FIGURE 4. Schematic diagram of the olfactory cell.

The olfactory region is yellowish to brown in man.

Physiologists[9] have noted that in a majority of the vertebrates a transition zone may be observed between the respiratory and olfactory epithelium. This intermediate zone may contain both ciliated and non-ciliated supporting cells. Many olfactory cells may be interspersed throughout the area.

Free nerve endings have been reported occurring in addition to the olfactory cells in the olfactory epithelium of vertebrates.[11] The source of these nerve endings are not settled, but it is assumed that they are of trigeminal origin.

The olfactory cells, or the end organs of smell (FIGURE 4) are the perceptive elements of the nasal mucous membrane and count almost 70 per cent of the cells present.[11] The other cells are restricted to supporting cells and numerous Bowman glands.

The olfactory cells are bi-polar and oval, with distinct oval nuclei.[10] Each of the olfactory nuclei are lodged in an oval cell body. Proximally the cell ends nearest the cribriform plate tapers into a nerve fiber and proceeds into an olfactory glomeruli (collection of many nerve fibers from several hundred olfactory end organs). Distally (toward the nasal cavity), the olfactory cell terminates in a small enlargement, called the olfactory vesicle. The vesicle of the olfactory cell carries many protoplasmic filaments, or hairs,[6,7,8] and these are integral parts of the cell.[5,10,11,13]

Many theories of olfaction[4] are dependent, or partially dependent, upon the penetration of the olfactory filament processes on the olfactory cell ends through the mucoid, or water layers, covering the olfactory epithelium. At present I do not know of any positive evidence showing that these olfactory filaments (human) protrude through the liquid epithelial covering, into the gaseous environment of the nasal cavity. Our experience is that it is extremely difficult to obtain olfactory tissue from cadavers, much less observe, or stain, the filaments with their natural watery covering. We cannot say with surety, therefore, whether or not these olfactory "receptor" filaments are bathed in a continuous liquid or gaseous environment.

Up to now we have viewed the nasal cavities of man to describe the area in general terms in order to illustrate the over-all structural environment wherein the olfactory organ occurs, and the special tissue environment of the olfactory end organs. There are other special considerations yet unmentioned which have a direct influence upon our over-all perception, or sensation, caused by inspired air.

Possibly it would be best to define the functions the nasal cavities fulfill for us. In animals the nasal area can best be defined by saying that the area serves as a survival "organ" (*i. e.*, the sense of smell), as well as a route for inspired air before it enters the lungs. In man the sense of smell is of secondary importance; the principal functions of the nose are primarily concerned with and attributable to the respiratory nasal parts and its covering fluids.

Previously, it was mentioned that (1) the conchae possess an ability to engorge themselves, or swell, and thus regulate the nasal volume; (2) cilia occur throughout the respiratory epithelium; and (3) numerous serous and mucous glands occur throughout the whole of the nasal chamber (excluding the vestibule). To bring these points together, we now must consider the liquid (serous or mucoidal in nature) sheath covering the entire nasal chamber, its sinus processes, and the numerous ducts. This sheath, or secretion, extends into the trachea, the pharynx, the esophagus, and down into the stomach. The whole sheath is in constant motion (normally) which, in the nasal area, is directed toward the nasopharynx.

The cilia cells, and gravity, produce the needed mechanical means to move this sheath at a measurable rate. The numerous serous and mucous glands are continuously secreting, so that the liquid sheath is replaced about every ten minutes, *i. e.*, over the posterior respiratory epithelium (see FIGURE 5).

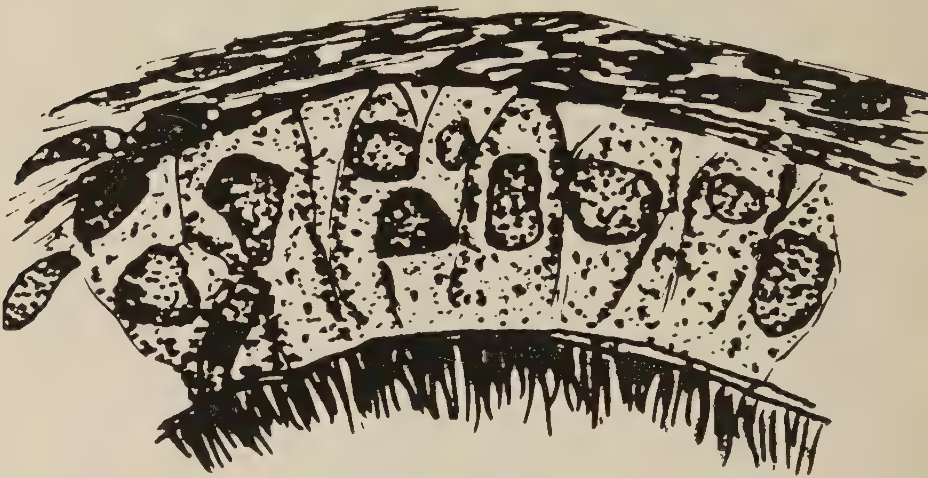


FIGURE 5. Ciliated columnar epithelium. Dimensions: ± 7 long, ± 3μ diameter.

The conchae, and this liquid sheath covering their surfaces, can accomplish the following functions:[9]

(1) Warm and humidify inspired air and, by performing this function,

(2) Regulate the air currents and air passages in the nose by reflex action.

(3) Filter many micro- and macroscopic particles from inspired air by liquid sorption and/or impingement. These particles are eventually carried into the stomach.

(4) Destroy, or prevent, infections to the nasal epithelium by a contained lytic enzyme, antibodies, and a normally low pH (*i. e.*, 5.5–6.5).[5]

(5) And, finally, by the combined actions of (2) and (3) above, cause the olfactory area of the nasal cavity to be sterile.[5,15]

The air we inhale is adjusted to ± 37°C before it reaches the glottis, while its humidity is raised to the saturation point before it reaches the lungs.[5] Air inhaled during normal breathing traverses the inferior meatus, and partially the middle meatus (see FIGURE 6). The upper olfactory area is outside of the main air current, and a change of breathing (sniff) is usually required to enhance or cause adequate eddying of air for olfactory stimulation.[1,6,11,15]

It has been noted that environmental variations, to induce temperature changes of the nasal mucosa, may effect the change in nasal volume (common meatus) and also pH of the nasal secretions.[5] If the nasal mucous membrane is lowered in temperature, a vasoconstriction is observed, while a rise in temperature of the membrane causes a vasodilation. A vasodilation indicates a larger nasal volume, while a vasoconstriction indicates a smaller volume to a complete closure. Temperature changes may also affect ciliary action and the movement of the watery sheath. The nasal secretions are varied in their pH by temperature changes of the mucous membrane. It has been noted that coldness produces a trend toward alkalinity.[5]

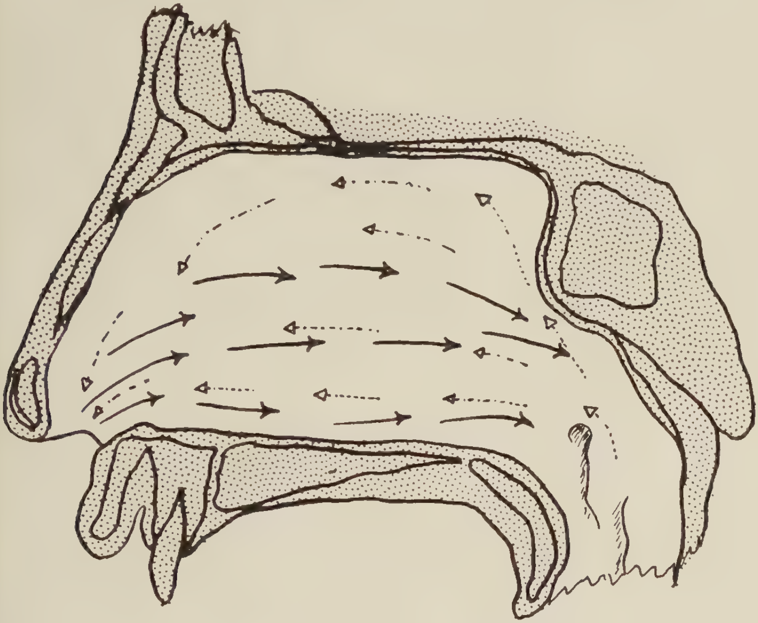


FIGURE 6. Schematic diagram of air currents and their direction. Solid arrow, inhalation. Broken arrow, exhalation.

When we speak of the olfactory receptor process, I again wish to point out that since our inhaled air (odorous or not) must traverse an indirect route before it can be "sampled" by the sense of smell, other sensations can precede, or accompany, the pure olfactory sensation. Spiegel and Sommer[13] have noted that the nasal mucous membrane of the nose possesses the sense modalities of pain, touch, heat, and cold in conjunction with that of smell.

Before actually discussing the receptor process, it is best to define some terms to be used:

(1) *Adequate olfactory stimuli* are chemical molecules possessing a certain volatility, a certain solubility (either in water and/or lipoids), and other physical characteristics necessary to allow them to reach the olfactory cleft and stimulate the end organs of smell.

(2) *Inadequate stimuli* are those stimuli (*i. e.*, those not specifically defined as olfactants) that "trigger" the discharge of olfactory end organs although they may not be odorous. Inadequate stimuli could be illustrated by an inert particle, making contact with a receptor end organ.

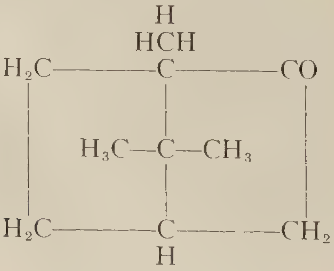
With regard to adequate stimuli, Professor E. D. Adrian of Cambridge has published some excellent experimental data and papers [1,2] to define the receptor excitation process of the olfactory epithelium. A significant conclusion arrived at by Adrian is that different types of chemical stimuli excite different parts of the olfactory epithelium. The differences in excitation patterns are partly due to the structure or layout of the olfactory area and to the type of stimuli itself. Thus, esters may tend to be more effective in the anterior olfactory area, and oils, further back. The points of Adrian's work which I need to stress for my subject are: (1) large scale differences of pattern of excitation for different odorants can occur over the olfactory epithelium; (2) the olfactory organ is apparently not a uniform mosaic of receptors; (3) the physical characteristics of the odorants seemingly play an important role in deciding what specific areas are activated; and (4) his work (and possibly that of others) have opened up many new possible avenues of olfactory research.

In 1951, after reading in the 1950 British Medical Bulletin of Adrian's latest work, I wrote and made some inquiries concerning his theory. A few months later we attempted a research program utilizing a modified adaptation selection technique. The procedure was to plot the "overlap" areas eventually strictly from subjective measurements.

The apparatus used, called a Multi-Stimulus Olfactometer, is of my own design. FIGURE 7 shows some of the basic parts of the olfactometer. Basically, the apparatus allows the operator to deliver one pure odor continually to an observer for adaptation purposes, then to introduce up to three other similar, but different, odors into that air stream, singly or together.

It would be too time consuming to show the complete technique employed in these studies, but to illustrate some of the chemical and physiological problems involved (excluding the subjective), let me take two simple odors from one large classification system. The odors are camphor and hexachloroethane, both of which possess but slightly divergent similar odors. The following diagram shows their structural formulas with some physical

Camphor—$C_{10}H_{16}O$



Molecular Weight 152.2

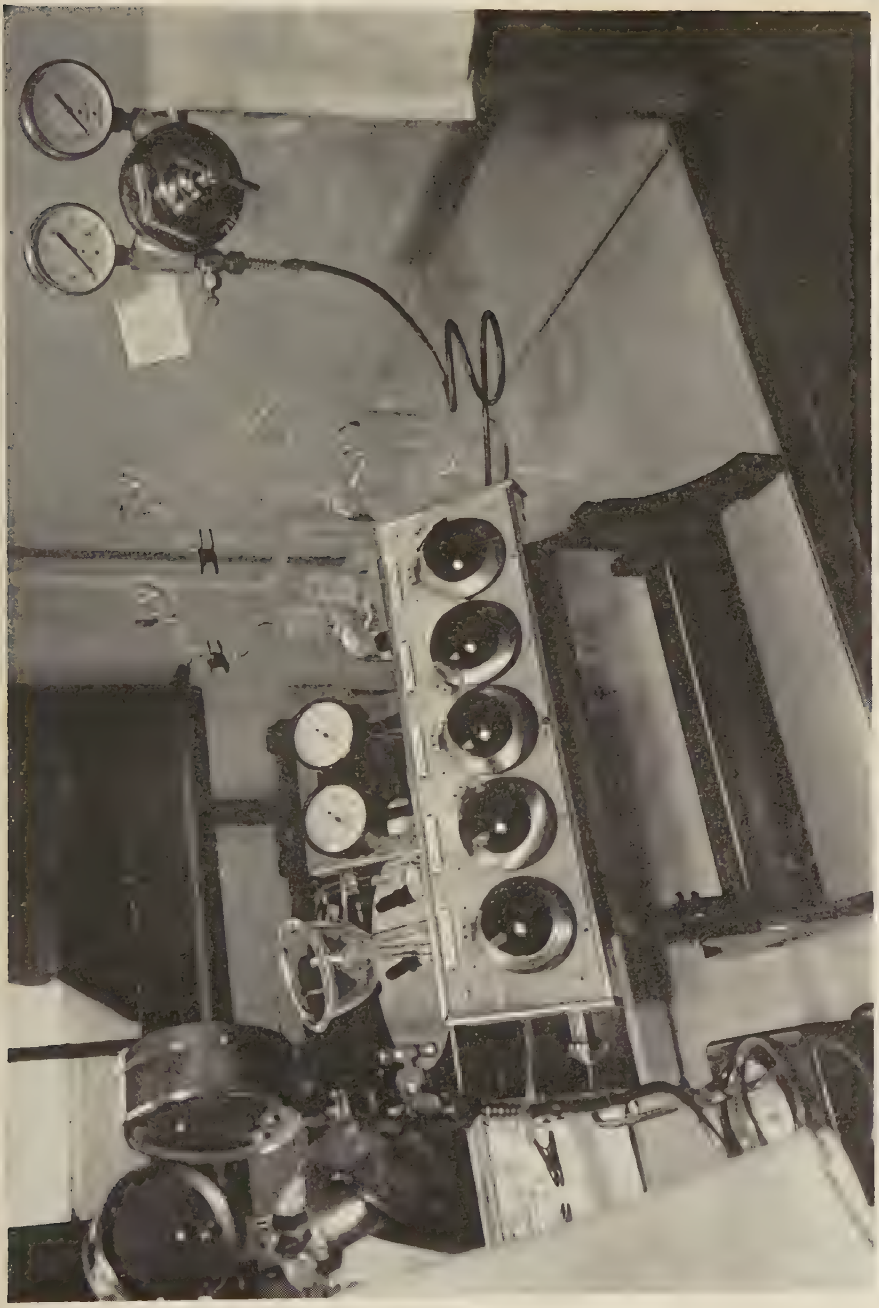
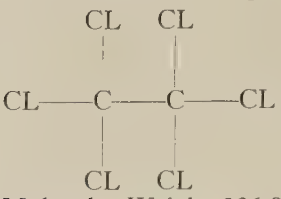


FIGURE 7. Multi-Stimulus Olfactometer.

Hexachloroethane—CCl_3 CCl_3



$$\begin{matrix} & \mathrm{CL} & & \mathrm{CL} & \\ & | & & | & \\ \mathrm{CL}— & \mathrm{C} & — & \mathrm{C} & —\mathrm{CL} \\ & | & & | & \\ & \mathrm{CL} & & \mathrm{CL} & \end{matrix}$$

Molecular Weight 236.8

characteristics. It is easier to see the spatial differences of the configurations using color discs attached in simulated molecular form.

The chemicals shown possess similar odors, but the molecules are entirely different. The problem is: Why does the nose detect a camphor note in hexachloroethane? Could it be that these two molecules excite the same receptor sites, or pattern, because of certain physical characteristics? Could it be that the spatial configuration (atomic distances) of these two molecules are similar? Could this be only a psychological mental phenomenon? We could go on forever if we so desired, but actually it would be best to explain something first.

We are not dealing with odor alone! Both of these chemicals excite, or arouse, other sensations in the nose. You can actually feel camphor when you inhale it and a sensitive nose can plot a mental schema of air travel. This same type of sensation occurs with hexachloroethane. It is my opinion, at this stage of my work, that if we could remove the extraneous sensory qualities from hexachloroethane, the pure odor component would not possess a camphor quality. I am also relatively sure that camphor itself possesses two (or more) sensory potentials, the odorous and the undefined sensations. This is an example illustrating extrasensory reaction in the nasal passage of certain odorants. I wish to point out, however, that this idiosyncrasy is not present in all odorants.

When we consider more complex odor systems, such as commonly occurring odors in living spaces, or industrial environments, we leave the realm of defining a pure odorant, which in itself is a broad term, to one of both adequate and inadequate stimuli. Here we find inert suspended matter and complex mixtures of odorants. Therefore, the olfactory receptor mechanism is greatly complicated with what I call inadequate stimuli (or inert suspended matter), whether for the sense modality of smell, touch, pain, or the like.

In 1838 Johannes Müller[3] postulated what has been termed the specific energies of nerves, wherein it was stated that the sensory end organs do not transmit image properties of a stimulus to the brain. The transmission is limited to electrical impulses, and a certain sensory receptor, say olfactory, can yield only one energy when excited, even if different types of stimuli are involved. Thus, both the adequate (or normal) and the inadequate (or abnormal) stimulus affecting an end organ can signal a similar response to the brain. The normal stimuli can be illustrated by a molecule from an odorous volatile chemical, for example, benzene; while the abnormal could be an inert aerosolized particle as described by Turk and Bownes in 1951.[14]

Likewise, the same argument may hold that certain chemicals called odorants may in fact involve other sense modalities as previously mentioned, wherein part of the odorant may serve as the "inadequate" stimuli for, let us say, the sensations of warm or cold, pressure or pain. Thus camphor, although possessing a definable odor part, can arouse a definite perception of coolness when inhaled at length. Another example is NH_3, since ammonia possesses a distinct odor. It can also arouse pain if inhaled in too severe concentrations.

Thus, when we come to defining the receptor process or mechanism for complex odor systems, we see that our task has been greatly magnified and complicated. We definitely deal with both adequate and inadequate stimulation of the sense of smell, and also those surrounding senses found in the nasal areas.

If we allow that Adrian's concepts are correct, in so far as saying that the olfactory region is laid out to respond selectively to odors, we must assume that the pure odorous components present in a complex air mixture simultaneously play over, or excite, a large area of the olfactory organ. Meanwhile, these same odorants can affect other sense modalities as inadequate stimuli. The other components of the air system, the inert particles of dust, aerosolized particles, *etc.*, may serve as inadequate stimuli for any or all of the sense modalities found in the nasal regions.

While speaking about the complexities induced by other components of a complex mixture of air and the possible sensations aroused from the nasal area, it is pertinent to note that the nasal or respiratory areas can be involved in many types of allergic symptoms ranging from the severely affected mucous membrane to merely an excess water discharge. In any case, odors have been observed to cause some reactions in themselves. If they act as protein or hapten antigens, this is open to debate, but in any case some of the reported cases [5,7,8] indicate that odors themselves may induce allergic manifestations. We can see, therefore, that some types of odorants can actually induce histo-pathological changes and, from the rapidity of onset of allergic symptoms, lead one to conclude that there is an extremely fast surface reaction between the excitant molecules and the mucous epithelium.

In a recent research project undertaken by Airkem, an attempt was made to define the complex odor systems involved in wood smokes. This was done by infrared analysis of a series of wood smoke condensates submitted to S. P. Sadtler and Son in Philadelphia. On final analysis we found, or identified, about 70 individual chemical components. There was also indication of many trace substances of complex structures which were undefined. It should be emphasized that these undefined trace components contribute significantly to what we call a "smoke odor."

Therefore, when we attempted to define the receptor mechanism of olfaction for only one complex odor system, it was more than obvious that we were dealing with an unlimited spectrum of possibilities. The pure odorants, we know, affect mostly the sense of smell, and these can be assumed to follow the route of selective area stimulation described by Adrian, wherein certain chemical components are specific for certain olfactory end organs or olfactory areas. The route of stimulation of separate olfactory end organs is as yet unknown, much less the specific sensations contributed by other variables. Most components of a complex odor system can enter the nasal passages, the more particulate and soluble fractions can be immediately sorbed into or onto the nasal mucous sheath and be carried with that sheath while it traverses the turbinate processes. The possibilities of changes in the pH of the sheath are great, and the affects of sorbed particles on the sensation of touch present many research possibilities to the interested student.

Another phenomenon common to the olfactory receptor process is the possibility of finding specific odors which tend to neutralize or counteract themselves when in combination. Since 1951, we have been better able to observe and define this occurrence. Basically this occurrence of odor pairing does not preclude the conclusion that chemical neutralization or intraction takes place in the air. Rather it involves the receptors, or receptor areas, themselves.

If two odors are found to be ideally paired, or antagonistic to one another, they can be presented in combination with one another in certain vapor concentrations where neither appears definable nor evident. If other odors, say of similar quality, are introduced into the same gaseous environment just described, they are usually immediately discernible. Therefore, the physiological process involved is not fatiguing or blocking certain receptor sites. The pairing of odors does not assume that the paired odors have to be similar or related in quality. On the contrary, some antagonistic odors appear to be startingly dissimilar when viewed according to present criteria.

At the present time we are investigating the odor pair technique strictly on the basis of chemical structure of molecules and their physical properties, and assume that some odor stimulation theory similar to that of Linus Pauling [12] can best describe, or define, what actually occurs at the receptor sites.

Odor masking is a common term to almost everyone. One odor is used to overpower, hide, or suppress the perception of the other. Using the Adrian spatial excitation theory, we can assume that olfactory masking is similar to that of auditory masking, where the intensity of response of the strongest excitant completely blots out the weaker, causing the temperal region to lose clear perception of the weaker excitant.

In conclusion, I wish to say that the sense of smell is one of man's finest analytical sensory apparatus. It is true that it only serves selected individuals at the present time, such as chemists, perfumers, *etc.* In the years to follow, however, we will observe that this sense has really lain dormant, rather than degenerating. The sense of smell can be developed to detect and identify an unlimited range of chemicals and specific parts of molecules. With our present-day emphasis on controlling our environment to promote longer life with greater health and mental ease, we have attempted to control the water we drink and the food we eat. Thus, the next logical phase will be to control and know the air we breathe, since our air comes into the most intimate contact with our bodies, and contacts the most adsorptive tissues possessed by the human body. Olfaction is the only one of our five senses that is capable of learning to define the worthiness of the air we breathe. This one provision can mean a lot to man in the future years when he may have to live in sealed, air-conditioned spaces, isolated from a completely polluted environmental air.

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THE AFFERENT NEURAL PROCESSES IN ODOR PERCEPTION *

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It is sometimes assumed that in order to understand the physiology of odor discrimination, we must first understand the mechanism by which the odor-producing molecule stimulates the receptor. This assumption is not warranted. Although it is true that the stimulus and receptor properties determine the first step in olfactory discrimination, these events are not the only determinants of the total process. In order that the highest centers of the olfactory system may receive differential discharges, every group of elements between the receptors and the ultimate receiving areas in the brain must also receive and transmit differential discharges. Thus, discrimination depends on the total system and anything learned about one of its parts contributes to the understanding of the system as a whole.

It is not too distressing, therefore, that electrophysiologists as yet have not been able to record directly from the primary olfactory fibers. They have turned instead to the differential discharge characteristics of the secondary fibers in the olfactory bulb. As a matter of fact, the behavior of the secondary neurones will reflect the discharge characteristics of the primary sense cells. Thus it should be possible to study indirectly the primary afferent cells by means of these "down stream" events. The present paper will review the afferent neural processes in the olfactory bulb as they have been uncovered by means of the electrophysiological method.

In any electrophysiological work the histology of the area being studied is important, but it becomes even more so when, as in the olfactory bulb, the elements giving the responses cannot be observed directly during the recording session. The proximal processes of the unmyelinated primary olfactory cells join just beneath the epithelium to form a series of longitudinal fasciculi which run back toward the cribriform plate (Read,[14] and Le Gros Clark and Warwick[12]). As soon as the plate is pierced, these primary neurones interlace in a complex manner on the bulb surface[13, 14] (FIGURE 1). Slightly deeper in the bulb the terminal ramifications of the primary neurones interlace with the dendrites of the tufted and mitral cells to form the olfactory glomeruli (FIGURE 2). These goblet-shaped clusters of fine nerve terminations are a unique feature of the olfactory bulb. In spite of the intricate intermeshing of nerve terminations, there is no continuity of primary and secondary neurones. As in all synaptic regions, there is merely physical contact between the surfaces of two neurones. The dendrites of the tufted and mitral cells then plunge deeper into the bulb where they reach their cell bodies. From here their axones travel longitudinally from the bulb. Alli-

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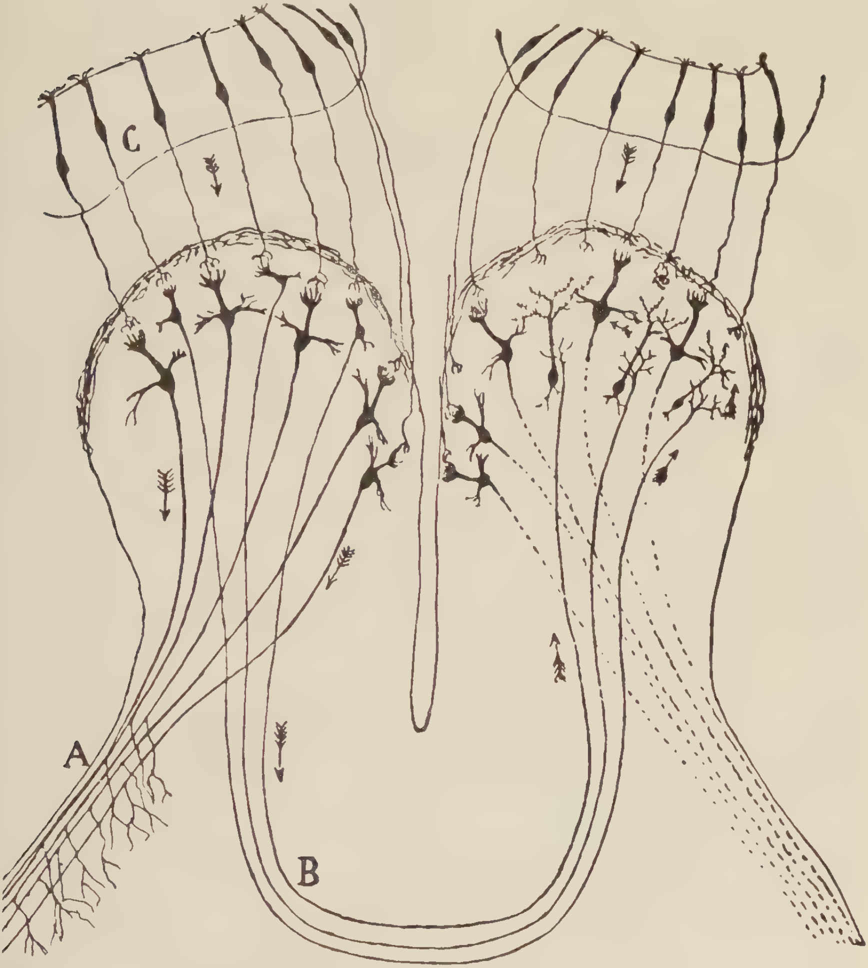

FIGURE 1. Diagram showing the lateral olfactory stria (A), the anterior portion of the anterior commissure (B), and the primary olfactory fibers (C). From Ranson and Clark,[13] p. 285.

son and Warwick,[9] who have studied these elements numerically, report that in the rabbit each bulb contains approximately 50,000,000 primary neurones, 1,900 glomeruli, 45,000 mitral cells, and 130,000 tufted cells. Therefore, these authors conclude that the glomerulus is anatomically an excellent mechanism for spatial summation since each glomerulus receives impulses from about 26,000 receptors and sends them on through only about 24 mitral cells and 68 tufted cells. Most of the mitral cell axones from the whole bulb then come together to form the 60,000 fibers of the lateral olfactory striae (this large figure probably includes some 15,000 extraneous fibers from the accessory bulb and some fine collaterals) which carry the impulses to higher centers of the brain. Most of the tufted cells make contact with the other bulb through the anterior portion of the anterior commissure (see FIGURE 1).

Adrian and Ludwig [8] first demonstrated the feasibility of electrically re-

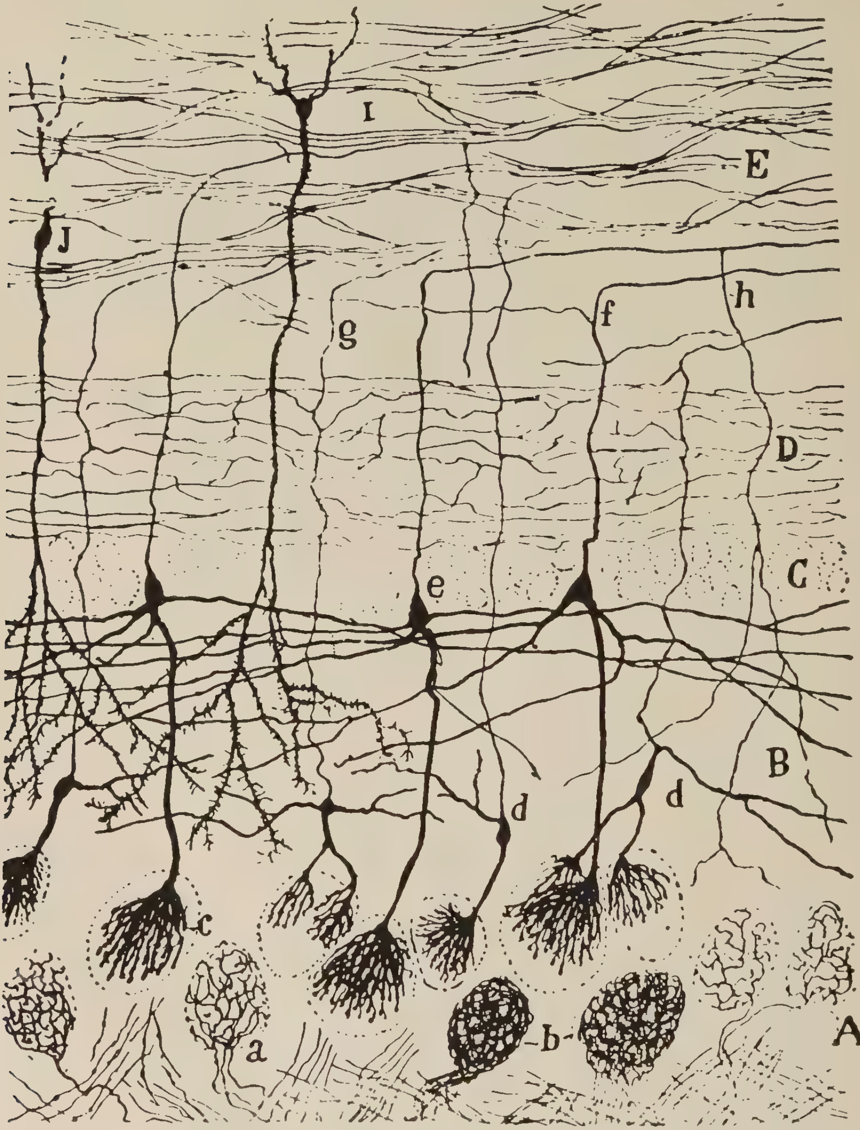

FIGURE 2. Section of the olfactory bulb of a kitten. Golgi method. A, layer of the glomeruli; B, external plexiform layer; C, layer of the mitral cells; D, internal plexiform layer; E, layer of the granules and white substance; I, J, granule cells; a, b, glomeruli, showing the terminations of the olfactory nerve fibers; c, glomerulus, showing the terminal arborization of a dendrite of a mitral cell; d, tufted cells; e, mitral cell; f, g, mitral cell axones; h, recurrent collateral from an axone of a mitral cell. From Ranson and Clark,[13] p. 286.

cording olfactory nerve impulses using the fish. In these organisms the olfactory tract is a long nerve-like stalk connecting the olfactory bulb with the forebrain and is readily accessible after appropriate dissection. Adrian has since continued the electrophysiological investigation of smell in such mammals as the hedgehog, rabbit, and cat.

The electrical activity of the bulb as a whole can be recorded by gross electrodes on the surface of the bulb. Fine insulated wire electrodes inserted into the bulb permit recording from various neural elements within the structure. These discharges are amplified about a million times so that oscillographs and other electronic recording equipment can be used. The electrical signs of neural activity vary from several microvolts to a few millivolts depending upon the preparation.

The amplifiers usually employed for such work are capacity coupled. Their output may be led into two oscillographs, one for photographic recording with a camera and the other for visual monitoring. In addition a loudspeaker may be inserted into the system so that the changes in neural activity may be monitored "by ear." In addition, electronic counters or integrating circuits may be employed. Essentially, an integrator is a device for electrically summating nerve discharges per unit time. The integrator drives an ink writer which traces out these summated discharges. As will become evident later, the integrator recording method is excellent for comparing the strength and the temporal course of neural activity in multi-fiber recording.

In Adrian's early experiments, the animals were permitted to inspire room air normally. Pieces of wool moistened with odorous material were placed before the nose or nose-piece. In later experiments the animal's trachea was cannulated so that air could be drawn through the nose by the suction of a small pump. Pure air or odorized air was brought to a funnel face-piece fitted loosely around the animal's snout. The stimulating air stream escaped into the room. Odor stimulation was controlled by the dilution technique. Compressed air from the laboratory supply was purified by absorbent charcoal. This air stream could be split two ways. One part passed over an odorous material contained in a flask and could be recombined in various proportions through a mixing valve with pure air. The odorized or pure air was led to the face-piece.

Essentially the same technique has been employed in the electrophysiological experiments carried out by the present authors. Calcium chloride and silica gel are used to dry and purify the air supply from a rotary air compressor. Odors may be changed by stopcocks which control the air flow through a bank of odor flasks. The odor stream is then diluted with pure air. Provision is made for cleaning all the glass apparatus with steam and hot purified air.

Adrian's early results with the hedgehog [1] seemed to show that the mitral cells discharge with synchronous volleys simply as a result of mechanical stimulation when air is drawn through the nose. The addition of odor increases the discharges but disrupts their synchrony. However, after further work with rabbits and cats and using filtered air with improved control of the stimulus, Adrian[3,6] later concluded that there is no mechanical stimulation under normal conditions. Rapid movement of large volumes of air through the nose can produce a discharge that may be due to material coming from the anterior parts of the nose itself.[6] In addition, it was found that the depth of anesthesia has a profound effect upon the discharges.

There are two kinds of waves evident in the bulb.[5] These are: (a) intrinsic waves attributed to the spontaneous activity of the cells of the bulb; and (b) induced waves elicited by olfactory stimuli such as amyl acetate, pentane, benzene, and ether. The waves can be recorded from the entire surface and more external areas of the bulb. There is an interesting interrelationship between the induced and intrinsic activity with changing anesthesia level. During deep anesthesia, the intrinsic activity is depressed and the train of synchronous induced waves following olfactory stimulation is readily apparent as shown in FIGURE 3. Under only moderate and light anesthesia, the continued activity of the bulb interferes with or disrupts the stimulus-produced discharges. As the anesthesia becomes still lighter, the olfactory-produced discharges again become clear. Never, however, are they as independent of the intrinsic activity of the bulb as under deep anesthesia. The present authors obtained similar results in the rabbit except that, under urethane anesthesia, frequencies of 10 to 50 cycles/sec. were obtained as compared with frequencies of from 50 to 60 cycles/sec. reported by Adrian under these conditions. No correlation between wave frequency and stimulus could be found.

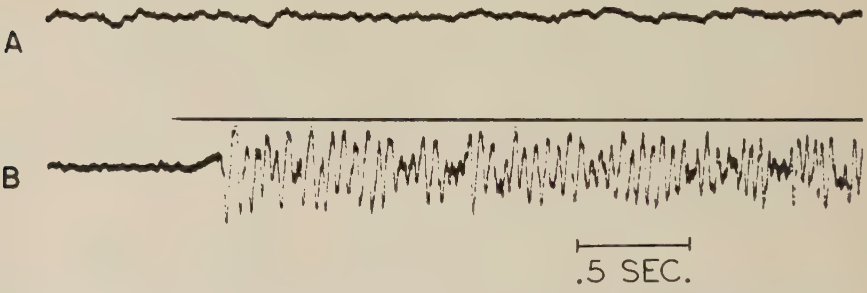

FIGURE 3. Typical wave response as observed by the present authors from the more dorsal areas of the olfactory bulb. A, stimulation with pure air; B, stimulation with amyl acetate. The black line above the records denotes the duration of the artificial sniff.

The relationship between the induced waves and another type of activity, the fast spike discharge, has been studied by Adrian.[5] By simultaneously recording from spike and wave areas, he finds that spikes appear first on stimulation to be followed by the appearance of the waves. Once the waves appear, however, the mitral cells from which the spikes are presumed to arise fire rhythmically with them. Nevertheless, the function of these waves is still not understood and the elements giving rise to them have not been clearly localized although Adrian places their greatest potential gradients between the outer glomeruli layer and the internal plexiform layer.

Quite recently data concerning waves in the human olfactory bulb has been obtained by Sem-Jacobsen, Bickford, Dodge, and Peterson[15] who recorded from the bulb of a psychotic patient while he was respiring room or odorous air. Tincture of valerian and benzene gave a series of rhythmic waves at each inspiration whereas ordinary air yielded no response. No correlation was found between the particular odorants and the wave frequencies which ranged from 28 to 32 cycles/sec. In several respects, however, their results differ from those previously mentioned. First, they found no spontaneous waves which are so obvious and consistent in the rabbit. Until it can be determined whether this is due to differences in procedure, the type and level of anesthesia, *etc.*, no species difference in this respect should be inferred. In the case of the human, administration of a barbituate anesthetic (thio-pental) abolished all responses whereas in the rabbit with other types of barbituates the bulbs continue to respond. It is interesting to note that Sem-Jacobsen *et al.* did not record any fast spike responses in the human olfactory bulb.

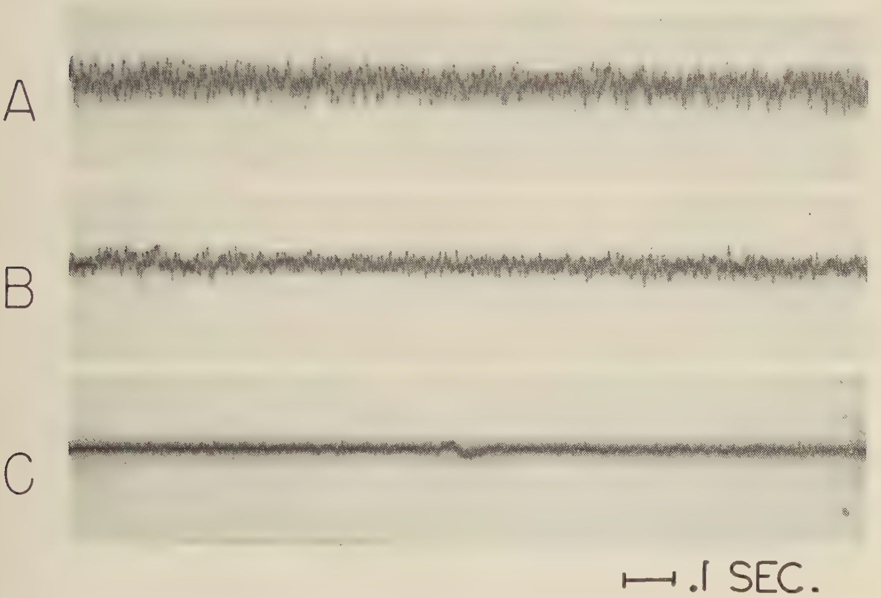

FIGURE 4. The effect of anesthesia on the spontaneous spikes from the deeper parts of the olfactory bulb. A, spikes under very light anesthesia; B, spikes after an additional two grams of urethane; C, spikes after another two grams of urethane.

Spike responses typical of myelinated neurones have been found consistently in lower animals when fine wire electrodes are thrust into the bulb.[1,3,4,5,7,8,16] Adrian places their upper boundary at about 1.5 mm. below the surface of the bulb in the rabbit. The upper boundary is placed at about 2 mm. in the anterior areas and about 2.25 mm. in the posterior areas in experiments carried out at Brown University. Such measurements would depend upon the size of the animals, and the discrepancy probably is not serious. Although it is generally assumed by all the authors involved in these studies that most of these spikes come from the mitral cells or their axones, it is well to keep in mind that some of this activity may be from other elements such as the glomeruli or tufted cells. Until the histological and electrophysiological techniques are combined to investigate the problem, there can be no certainty regarding the types of response yielded by the various bulb elements.

The relation between spike activity and the depth of anesthesia is much like the one found for the wave activity (see FIGURE 4). During light and medium anesthesia (A), there is a large amount of spontaneous activity which appears to last indefinitely. Even stimulation does not seem to affect the activity although under very light anesthesia small responses can be seen against the unstable background on the integrator record. However, as more anesthesia is administered, the spontaneous activity is gradually lowered (B) and the responses become more observable. Finally there is little or no spontaneous activity, and the spike discharges to odorous stimuli become quite discernable. FIGURE 5 shows such a spike response to heptane whereas in the case of pure air stimuli no discharge is seen.

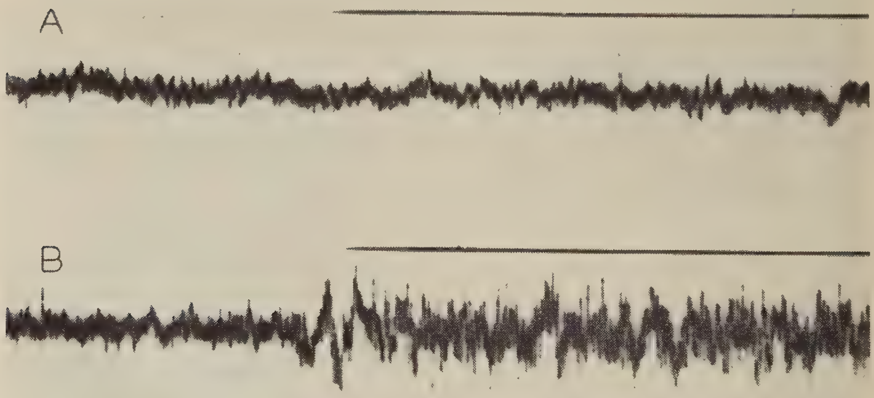

FIGURE 5. Typical spike discharges from the deeper aspects of the olfactory bulb. A, stimulation with pure air; B, stimulation with heptane. The dark black line above the records denotes the duration of the stimulus.

An interesting feature of the anesthetic effect is that the lighter the anesthesia, the longer the response is, except perhaps for the very lightest levels. In fact, at one point in this continuum from deeper to lighter, the response to a stimulus will last indefinitely but can be terminated by the administration of more anesthesia.

Under an appropriate level of anesthesia a regular discharge of impulses can be detected at each inspiration of room air whereas no discharge occurs with purified air. This response appears to result from faint odors in the room. Such discharges may continue for many hours giving no sign of adaptation. Since adaptation to odors is so typical of the sense of smell, this finding is surprising. Adrian [6] suggests that olfactory adaptation is not due to a failure of the sense organ but perhaps to some central process.

Of particular interest to the mechanism of odor discrimination are Adrian's findings showing differential activation of the olfactory bulb by different chemicals.[2,3,4,6,7] In the rabbit, water-soluble substances, such as amyl acetate, ethyl acetate, ether, and acetone, in low concentrations produce mitral cell spikes in the anterior part of the bulb. These fibers are said to synapse with the primary fibers from the forward and dorsal parts of the olfactory epithelium.[3] Substances such as pentane, coal gas, and benzene which are appreciably soluble in lipoids produce discharges in the posterior part of the bulb when presented in low concentrations. The mitral cells here make contact with the fibers from the ventral and aboral parts of the epithelium. The cat shows the same type of areal sensitivity with the addition of a more dorsal posterior region which is most sensitive to trimethylamine.

There seems to be, therefore, an areal correspondance between stimulus, epithelium, and the bulb. At first the work of Le Gros Clark and Warwick [12] seemed contrary to this interpretation. They observed retrograde degeneration of the septal mucosa after partially or completely ablating the bulb and found a general thinning out of the receptors rather than a localized loss. When, however, Le Gros Clark later repeated this work [11] on the whole of the epithelium rather than just the septal area, he found evidence supporting areal representation in the epithelium corresponding to different areas of the bulb.

In addition to the spatial differentiation, Adrian also reports a temporal differentiation. Responses to amyl acetate, for instance, occur with a shorter latency and are more abrupt in their growth and decay than the longer latency responses to pentane which rise and fall more gradually.

It appears, therefore, that, at least with low concentrations, discrimination of odors might occur on the basis of two differentiations in the impulses being sent from the bulb to the more central olfactory processes. First, there is the area of the bulb from which the impulses come. Secondly, there are the temporal discharge properties such as latency, build-up time, and decay time. If the large number of temporal and areal characteristics are taken to function simultaneously and each chemical gives rise to a slightly different combination, this might provide a mechanism by which the more central areas could differentiate among odors. The problem of discrimination becomes more complicated, however, because the clear areal specificity is apparent only at very low concentration. Parts of the bulb which previously had not been stimulated by certain substances at low concentrations can be made to respond to higher concentrations of the same substances.[3,4,6] Although an increase in the concentration affects the areal differentiation, Adrian found that concentration does not affect the temporal pattern.[4]

Such results suggest that at higher stimulus concentrations there is a gradient of activity across the bulb. As the concentration is increased, those regions or units that respond first to the lowest concentrations of a chemical will respond with a greater discharge as other regions or units become activated. Thus, the spatial differentiation is relative rather than absolute, perhaps in a manner much like that found by Galambos and Davis[10] for the sense of hearing. At certain concentrations, a hydrocarbon-like heptane may stimulate the anterior bulb more than will an ester like amyl acetate. However, when these same concentrations are employed in the posterior bulb, the hydrocarbon will be relatively even more effective than the ester. Thus the spatial differentiation can best be described in the case of amyl acetate and heptane by a ratio of the response magnitudes to these two substances in the front as compared with the back.

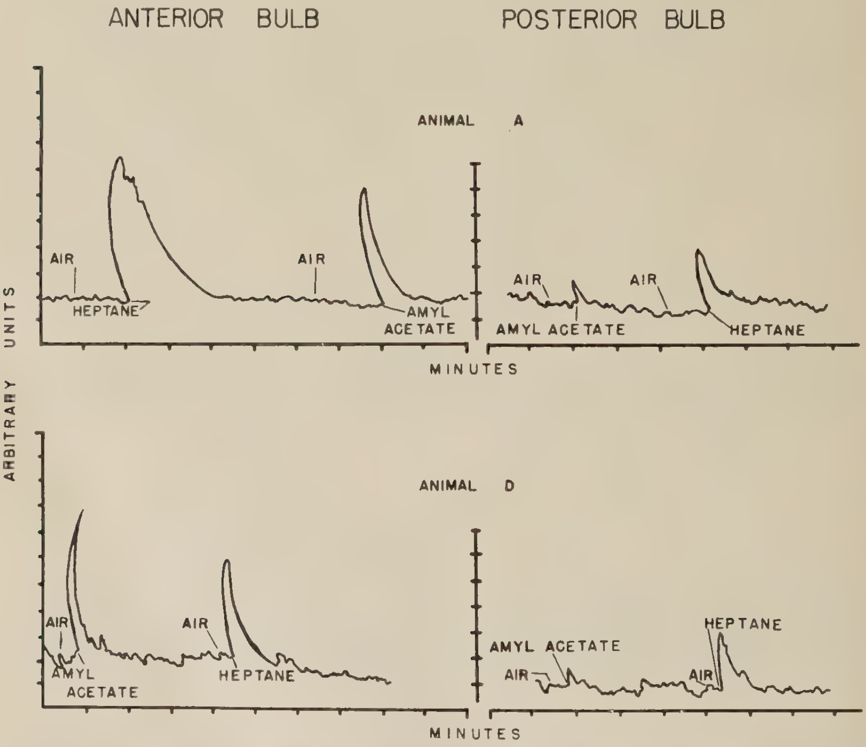

FIGURE 6. Integrator records of the spike discharges from the anterior and posterior areas of the bulb following stimulation by heptane and amyl acetate each of which is maintained at a constant concentration for each one of the animals (A and D). Both animals display an areal and temporal differentiation.

In order to measure such effects, the discharges must be observed and quantified. The usual oscillographic technique is not so well adapted to this purpose as is the integrator described above. The ink writer records so obtained by the present authors (FIGURES 6 and 7) can be compared for the strength and time course of the responses.

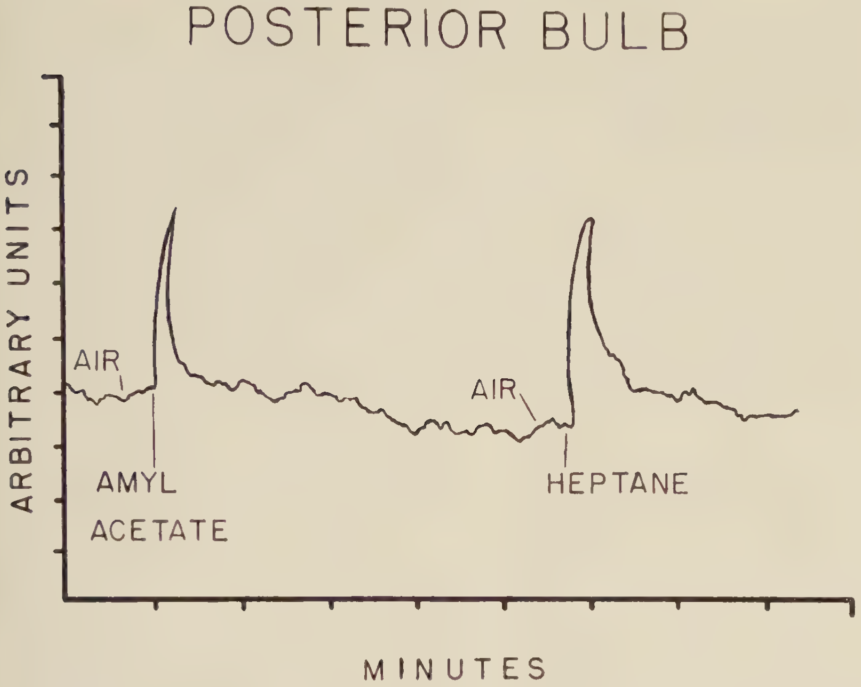

Figure 7. Integrator record of the spike discharges from the posterior bulb after the concentration of amyl acetate was made large enough to give a response equal to the heptane response. The temporal differentiation is shown.

Table 1

The Average Magnitude of Responses (in Arbitrary Units) to Amyl Acetate and Heptane from the Anterior and Posterior Olfactory Bulb in Five Rabbits

		Anterior			*Posterior*		
Animal	*Number of comparisons*	*Amyl acetate*	*Heptane*	*A:H ratio*	*Amyl acetate*	*Heptane*	*A:H ratio*
A	4	9.5	10.8	.88	5.9	12.9	.46
B	6	6.3	0	Inf.	0	12.4	0
C	7	9	7.6	1.18	5.1	12.8	.40
D	7	21.8	17.9	1.22	4.3	9.3	.43
E	9	5.5	8.3	.66	8.2	25.4	.32

The results with this method are shown on table 1. The average magnitude of the response to amyl acetate and heptane from the anterior and posterior portions of the bulb are tabulated for five rabbits. In animal A the average magnitude of anterior response to amyl acetate was 9.5 units and to heptane 10.8 units. Thus, amyl acetate yielded a smaller response than did heptane. A ratio can be computed by dividing the amyl acetate response by the heptane response. In this case the A:H ratio is 0.8. A ratio of 1.00 indicates equal response magnitudes. A ratio of greater than 1.00 indicates that the amyl acetate response is larger. In two cases in the anterior bulb, the amyl acetate response is less than that to heptane; in three cases, the amyl acetate response is greater. In the posterior bulb, heptane yielded a greater response in all cases. In one animal (B), heptane did not activate the anterior bulb at all whereas amyl acetate did not affect the posterior bulb. In this case, however, the animal was under very light anesthesia so that the responses to stimulation occurred against a background of spontaneous activity which may have masked responses of small magnitude.

These results indicate that, although the hydrocarbon always gave larger responses posteriorly, the converse (that it would give smaller responses anteriorly) was not always the case. On the other hand, *in any one animal* the A:H ratio was always larger in the front than in the back. This is graphically shown in FIGURE 8, and is illustrated by tracings of the integrator records in FIGURE 6. The amyl acetate response dropped proportionately more from front to back than did the heptane.

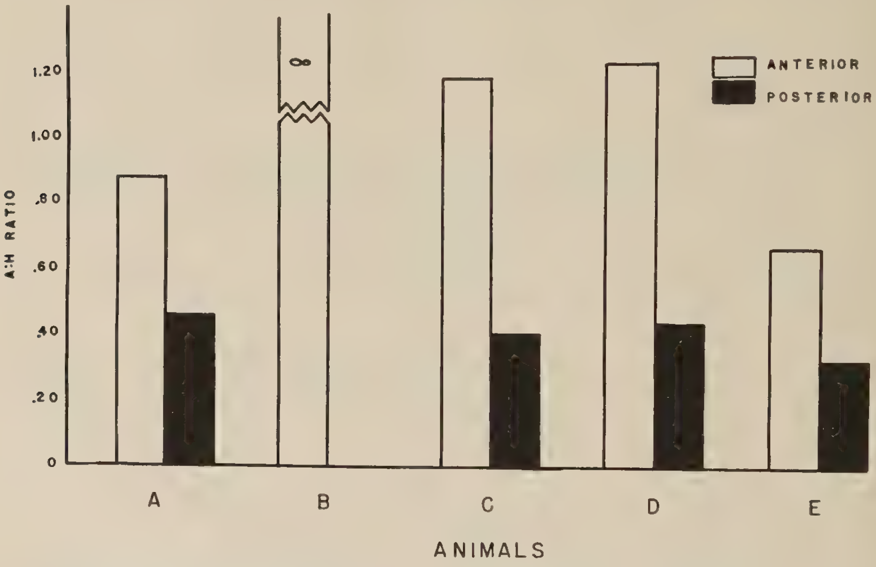

FIGURE 8. Graphical comparison of the ratios of amyl acetate to heptane response magnitude (A:H) from the anterior and posterior bulbs.

FIGURE 6 illustrates the temporal characteristics noted by Adrian. Different stimuli may show responses with clear temporal differentiation. Since the paper speed of the ink writer is quite slow, little can be said about the latencies of the fiber discharges, but the tracing does show graphically the temporal pattern in the growth and decay of the discharges. All stimuli are presented for equal durations of about 0.4 sec. In the anterior bulb (animal A), the response to heptane is of longer duration than that to amyl acetate. The amyl acetate tracing comes to a sharper peak than does the heptane, indicating both faster rise time and faster decay time. That this temporal differentiation is not due to the larger response height to heptane is shown by the record from animal D. Here the amyl acetate is larger in height but is about half as long in total duration than the heptane response.

It is interesting to note that the respective responses are much shorter for animal D than for animal A. This, as stated above, is probably a function of anesthetic level. Nevertheless, it is quite apparent that, within any one animal, the two stimuli give rise to responses with differential time characteristics. Unfortunately the amyl acetate response is so much smaller than that of the heptane in the records from the posterior bulb that a comparison is very difficult to make. If, however, the amyl acetate concentration is raised so that its response nearly equals the heptane response such a comparison can be made. FIGURE 7 shows the results of this experiment. The same general characteristics found in the anterior bulb for these stimuli are evident in the posterior portion.

The spatial differences described above, however, are rather gross. They may be due to certain physical chemical properties like volatility or solubility in oil or water which might determine the ease of penetration into the deeper parts of the nasal passage.[3] In view of the multiplicity of odors and the great numbers of nerve cells and fibers in the bulb, we might expect that a more discrete differentiation of function takes place among the individual cells. In Adrian's most recent work such differentiation appears to occur.[7] By recording with very fine wires, responses are obtained from what appear to be single mitral units. In such instances, it is possible to find one substance that at a low concentration will excite a particular unit without affecting the other units in contact with the electrode. Other substances in low concentration will activate the other units. Such selective sensitivity is usually greatest for one substance (as, for example, benzene), but it may also be present to a lesser degree for related substances, such as toluol and xylol. Adrian, however, warns that there is wide variation in specificity and it is unlikely that the receptors are sharply divided into a limited number of classes.

It is clear from this review that the afferent neural processes underlying olfaction show evidences of differential activity that includes temporal and gross as well as detailed differentiation in the spatial pattern of response. It is not possible, as yet, to show just how each of these factors interact in mediating olfactory discrimination. As the data accumulates, particularly on the behavior of the individual mitral cells, some grouping of stimuli according to their physiological effect should emerge. Adrian [7] has already found that at least four main groups of olfactory stimulant can be distinguished: (1) aromatic hydrocarbons, (2) paraffin hydrocarbons, (3) terpenes and related substances, and (4) ethereal esters and ketones. However, these groups could be subdivided and others probably could be added. At any rate, it is to be hoped that continued research in this field utilizing electrophysiological methods will provide basic insights into afferent neural mechanisms underlying odor perception.

Summary

The present paper has reviewed both the histology and the physiology of the olfactory bulb with particular regard to the studies carried out with the electrophysiological technique. Most of the latter material is based upon the work of E. D. Adrian. Although this method is so far applicable only at the level of the secondary olfactory neurones, it has been shown that much information concerning the differential character of the olfactory responses could be obtained. There is both temporal and spatial differentiation of activity in the bulb. The spatial differentiation may be observed at a gross level such that the anterior bulb in the rabbit yields relatively greater activity to some classes of odorants than to others. This spatial differentiation is maintained with suprathreshold stimuli in terms of the relative magnitudes of responses to different substances in different regions of the bulb. Studies of activity in the individual mitral cells indicate that there is a selective sensitivity for one substance or closely related substances. However, it does not appear likely that there are only a limited number of primary receptor types. As Adrian says, the evidence suggests that odor discrimination depends upon the "cooperation of a number of factors giving information about different properties of the stimulating agent." [6]

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FUNCTIONS OF THE "OLFACTORY BRAIN"

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I. Definition of "Rhinencephalon"

Renewed interest in the "olfactory brain" or "rhinencephalon" has been provoked by the suggestion that in mammals this portion of the brain serves emotional rather than olfactory functions. Recent theoretical and experimental studies have examined various aspects of this suggestion. There has arisen a certain amount of confusion due to discrepancies in results. Furthermore, authors vary in their conceptions of what constitutes "emotion"; and they differ widely in their definitions of which morphological formations are to be subsumed under "rhinencephalon."

Some of the confusion may be traced to differences in results when different techniques are applied; a generalization from the data derived with one technique may not be substantiated by data derived with another technique. Discrepancies of fact may sometimes be resolved by considering the reliability of data (*i. e.*, the number of subjects used; the number of investigations reporting essentially similar results; and significance of the results if statistical techniques are applicable). At other times, the adequacy of the report must be taken into account (*e. g.*, comparing cerebral ablation studies without anatomical verification of lesions with those where such verification is reported). Usually, discrepancies can be resolved only by further experiments; ignoring them is least likely to encourage such experiments.

In this review, "emotion" is dealt with as an inference from behavioral data; speculations regarding emotions based solely on neuroanatomical data assume a greater knowledge of the biological variables determining emotion than we possess.

Choice of data is implicit in any survey of this scope and depends on the framework chosen for discussion. Whenever we are aware of them, such implicit choices will be made explicit. Thus, whether a neural formation might be subsumed under a definition of "rhinencephalon" depends in part on whether the reference is "olfactory function," or "emotional behavior," or both, as in this review. This first section deals, therefore, with our definition of the neural formations which are to be included in the "rhinencephalon."

The term "rhinencephalon" was first used by Kölliker [84] to denote a group of cerebral structures which, though apparently cortical, could be easily differentiated from the rest of the cerebral mantle. Meynert [106] had distinguished between cortex with gray surface and cortex with white surface: the latter constitutes Kölliker's "rhinencephalon" and is found in the "olfactory lobe," "hippocampus," and "septal region." The conception that these structures are related to each other and to olfaction came from studies of comparative and ontogenetic morphology. In subreptilian vertebrates, the entire forebrain is interspersed with a large mass of fibers originating in the olfactory bulb or anterior olfactory nucleus.[64, 79] In reptiles, although fibers originating in other systems become more prominent, the forebrain is still "dominated" by olfactory connections.[64] Those neural components of the forebrain which are recognizable in submammalian vertebrates can also be distinguished in mammals, although other, "newer" formations are added. In terms of the presumed order of their appearance, the divisions of the mammalian brain have been classified as "archipallium" ("hippocampus"), "paleopallium" ("olfactory lobe" and probably "septal region"), and "neopallium."[64] A body of evidence relating the size of structures subsumed under archi- and paleopallium to the size of peripheral olfactory structures has been summarized by Kappers *et al.*[79]

Classification invariably runs into difficulty with junctional or transitional categories. Thus, in the case of pallial formations, it is often difficult to distinguish hilar cortex from subcortical masses, *viz.*, in the amygdaloid complex and in the septal region. Another difficulty in classification arises in distinguishing between neocortex and "older" cortex. At the turn of the century, the biological generalization that "ontogeny recapitulates phylogeny" became current.[61] Brodmann[29] and the Vogts and their pupils[157] used Nissl's method for selectively staining cell bodies to make ontogenetic comparisons of cortical stratification in an attempt to resolve difficulties in classification. As can be seen from the recent review of these studies by Bailey and v. Bonin,[15] they were only partially successful. However, their conclusions, in general, support the distinction between new and older cortical formations. The former, which pass through a developmental six-layered stage, were termed "isocortex"; the latter, "allocortex."

There remain, however, large areas of cortex which are not readily placed into one or another of these categories. One such area, the cingulate gyrus, does not pass through a six-layered developmental stage but approximates the appearance of isocortex in the adult. M. Rose[134] suggested the term "mesocortex" to designate this area. A still more useful suggestion is that made by Filimonoff[45] who finds a transitional zone of cortex (both in development and in the adult brain) to separate typical allo- and isocortex along the entire length of the junctional boundary. He designates this transitional cortex (including that of the cingulate gyrus) "juxtallocortex." This suggestion is congruent with the cytoarchitectonic descriptions of v. Economo[43] and has been adopted by Bailey and v. Bonin. We shall follow them in referring to this cortex as juxtallocortex.* In mammals, and especially primates, the increase in the size of isocortical relative to allocortical formations is shared by the increased development of the juxtallocortical transitional areas. Thus, allocortical and juxtallocortical structures form a ring around the hilus of the hemisphere. This ringlike formation was the basis upon which Broca[26] and others, reviewed by Elliot Smith,[142] anticipating cytoarchitectural studies, grouped the hilar structures under the term limbic lobe. Support for this grouping has come not only from cytoarchitectural comparisons based on Nissl techniques, but also from the studies of Cajal [33] and Lorente de Nó [94, 95] which, using silver staining methods, compared the minute fibro-architecture of these limbic portions of the cerebral mantle with some of those of the lateral cortex. Current interest in the relation of cortex to emotion has encompassed structures which can be discussed only if the definition of "rhinencephalon" includes juxtallocortex as well as allocortex. This review is concerned, therefore, with all cortical formations not *typically* isocortical: *i.e.*, those which do not definitely pass through a six-layer stage in ontogeny. A variety of structures make up the "rhinencephalon" when it is defined in this manner. On morphological grounds, the following units can be distinguished:

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* However, we do not wish to follow Bailey and Bonin in classifying juxtallocortex as isocortex.

1. The *olfactory tubercle* is synonymous with the anterior perforate substance in primates.
2. The *prepyriform cortex* is the area surrounding the lateral olfactory tract. Because of current usage in primate literature, this term is preferred to "anterior pyriform," which is often used to describe the homologous cortex in macrosmatic animals.
3. The *amygdaloid complex* lies caudomedial to the prepyriform cortex and may be subdivided into corticomedial and basolateral groups. The former is also referred to as the periamygdaloid cortex. These terms are preferred to pyriform or posterior pyriform which usually refer to the same structures because occasionally the latter are used to include the entorhinal cortex.
4. The *frontotemporal cortex* is a junctional band of cortex lying between prepyriform and periamygdaloid cortex and orbitofrontal and polar temporal isocortex. Synonymous with orbito-insulo-temporal cortex, "frontotemporal" is preferred because of brevity.*
5. The *area of the diagonal band* is the cortex surrounding the medial olfactory stria.
6. The *septal region* has the same gross anatomical relationship to the area of the diagonal band as the amygdaloid complex has to the prepyriform cortex. The septal area refers to the cortical portion; septal nuclei to the subcortical portion of the region.
7. The *subcallosal area* is a junctional band of cortex lying between the area of the diagonal band and septal nuclei on the one hand, and the mediofrontal isocortex on the other.*
8. *Ammon's formation* is composed of the hippocampus and adjacent structures, the subiculum and fascia dentata.[128] The term Ammon's formation is preferred to hippocampal formation because the latter has been used by some to include the hippocampal gyrus Hippocampal gyrus has in turn been variously used: some authors include only entorhinal cortex; others include isocortex and the amygdaloid complex as well.

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* Evidence regarding the histogenesis of the frontotemporal (unit 4) and subcallosal juxtallocortex (unit 7) is relatively scanty. These transitional areas are given status apart from isocortex for heuristic reasons. See below page 113 for further discussion.

9. The *entorhinal cortex* and adjacent *presubiculum* constitute a junctional band of cortex lying between Ammon's formation and temporal isocortex.

10. The *cingulate* and *retrosplenial areas* are a junctional band of cortex lying between the supracallosal hippocampal rudiment (synonym: induseum griseum) and medial frontoparietal isocortex. "Cingulate" is preferred to the term "limbic" because the latter is sometimes used to include the entorhinal cortex and Ammon's formation.

II. Classification of "Rhinencephalic" Systems

A. Ontogenetic Histology

These heterogeneous morphological units which have been grouped together "by exclusion" (*i. e.*, by failing to meet the criterion defining isocortex) need not, *a priori*, serve homogeneous functions. It seems fruitful, therefore, to attempt some classification of these units into systems prior to a discussion of function.

Table 1

M. Rose's Histogenetic Classification (Simplified)

I. Totocortex:
  A. Holocortex: isocortex; cingulate and retrosplenial mesocortex; Ammon's formation.
  B. Schizocortex: entorhinal cortex.
II. Semicortex: olfactory tubercle; area of the diagonal band; septal area; prepyriform cortex; periamygdaloid cortex.
III. Bicortex: insular cortex.

M. Rose[132,133] has presented thoroughly documented histogenetic studies in an attempt to make such a classification (see TABLE 1). All cortex is derived from a migration of cells originating from centrally located nuclear masses of the forebrain. Rose pointed out that in some places practically all of the cells partake in this migration while in other places large nuclear masses remain behind. He labeled cortex formed from such "partial" migration as semicortex; it corresponds roughly to paleocortex (as defined phylogenetically). He labeled cortex formed when a "total" migration takes place as totocortex. This term subsumes a variety of structures including all of the isocortex, the cingulate mesocortex, the entorhinal cortex, and Ammon's formation. The totocortex was subdivided into "split" and "whole" types on the basis of relative contiguity of the migrated strata of cortical cells. Schizocortex (split), as in the entorhinal region, shows a split between the outer and inner layers; holocortex (whole) is found in Ammon's formation, the cingulate region and in isocortex. The various types of holocortex are distinguished on the basis of the number of cortical layers formed—respectively, two, five, and six. Rose, assuming the claustrum, an incompletely migrated formation, to be part of the overlying insular cortex, had to give special status to this formation ("bicortex"). Beck[18] has criticized the histogenetic findings upon which Rose's classification is based;

unfortunately he has so far failed to substitute a more tenable one. Filimonoff,[45] on the other hand, although similarly critical of Rose, places emphasis on the aforementioned transitional bands of cortex, and thus provides an alternative basis for classification. In agreement with other cytoarchitectonicists he distinguishes iso- from allocortex on the basis of the early development in the former of six recognizable layers. He places Ammon's formation in a separate allocortical category (archicortex) and suggests that the presubicular and entorhinal areas form a juxtallocortical (periarchicortical) formation which includes not only the usually recognized temporal portion but also supracallosal and retrosplenial portions (Rose's cingulate mesocortex). Thus, in spite of his criticisms of Rose's classification, Filimonoff, on independent grounds, comes to include in related classes (archicortex and periarchicortex) those allocortical structures which Rose had grouped as totocortex.* Filimonoff also agrees with other cytoarchitectonicists, including Rose, in grouping together, as semicortex, the olfactory tubercle, diagonal band, septal area, prepyriform cortex, and periamygdaloid cortex; however, here again he differs as to the basis of classification. Only with respect to the insular cortex does this difference result in a change. Because he disagrees with Rose regarding the cortical nature of the claustrum, Filimonoff is free to classify parts of insular cortex with parts of the remainder of the cerebral mantle. A band of transitional cortex abutting semicortical formations has been described repeatedly.[24, 43, 45, 78] This delineation of a frontotemporal and subcallosal juxtallocortex (perisemicortex) appears useful in subsuming available anatomical and physiological data.

Summary. It is apparent that, although several authors use separate histogenetic criteria (and only Rose has stated his explicitly), similarities in final classification appear. Two major divisions of allo- and juxtallocortex may be distinguished. One includes the olfactory tubercle, area of the diagonal band, septal area, prepyriform and periamygdaloid cortex, and the surrounding subcallosal and frontotemporal transitional cortex. The other includes Ammon's formation and its surrounding transitional cortex: the entorhinal cortex of the temporal lobe, and the pericallosal cingulate and retrosplenial cortex. This classification supports the comparative anatomists' distinction between paleo- and archicortex, but suggests that the newer transitional formations be classified together with the adjacent older cortex rather than with the rest of the neocortex. Further evidence supporting the utility of this classification comes from a study of anatomical relationships *between* these several structures.

B. Axonographic Anatomy

A large body of evidence concerning the interrelationships between the several morphological units which are considered in this review has been accumulated by observation of stained "normal" brain sections. Therefore, before turning to the somewhat more reliable and often more specific information derived from experimental material, an attempt will be made to cover the extensive literature based on observation of normal tissue.

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* The argument with respect to inclusion of the isocortex in this category does not concern this review.

Fibers are seen leaving the olfactory bulb (which receives the olfactory fila from the receptor) to course caudally, some terminating in the olfactory tubercle,[40,75,79] and others crossing to comparable structures in the opposite cerebral hemisphere via the most rostral fibers of a large tract, the anterior commissure.[28] At the level of the olfactory tubercle, the fibers split into two major tracts, a medial and a lateral olfactory stria.

The medial stria can be followed into the subcallosal and septal regions. It appears, however, that these latter structures do not receive fibers directly from the bulb. Fox[46] found that, in the cat, major connections originate *only* from the olfactory tubercle. From the septal region, fibers can be traced to the area of the diagonal band and, perhaps partly through relay in this area, to the amygdaloid complex. Another major outflow of fibers from the septal region apparently reaches the habenular nuclei (of the epithalamus) via the stria medullaris, a conspicuous tract probably formed by fibers from other medial structures (especially amygdaloid complex and anterior hypothalamus). (See review by Brodal.[27])

The lateral olfactory tract can be traced to the prepyriform cortex and to the amygdaloid complex.[60,66,74,115,165] From this complex a large outflow of fibers, the stria terminalis, apparently connects to the septal region and anterior hypothalamus. Connections between the amygdaloid complexes of the two sides have also been described to course in the stria terminalis as well as through the anterior commissure. Some of the fibers of the stria are also said to join the medial forebrain bundle to reach structures in the posterior hypothalamus.[46,79,165]

The observations relating the other components of the limbic lobe (juxtallocortex and Ammon's formation) to the olfactory afferents are more tenuous. Fibers from the olfactory bulb and anterior olfactory nucleus, via the medial olfactory tract, have been described by a number of authors[46,60,66,74,79,165] to reach the anterior end of the supracallosal hippocampal rudiment, a structure believed to be vestigial and distinct from the major portion of Ammon's formation, especially in mammals. Most reports are cautious in their descriptions. Thus, Fox states that fibers appear to "enter into relation" with the hippocampal rudiment. No direct connections between olfactory bulb and cingulate or entorhinal cortex have been claimed.

On the other hand, the interrelations between cingulate and entorhinal cortex and Ammon's formation are better established. Cajal[33] and Lorente de Nó[94,95] described afferent fibers to Ammon's formation from the cingulate cortex via the cingulum and supracallosal stria and from the entorhinal cortex via "alvear" and "perforant" paths. From Ammon's formation emerges a large tract, the fornix. This tract apparently connects with the septal region and the mammillary body of the posterior hypothalamus.[46,66,165] Other connections have been described, including the hippocampal commissure which relates the hippocampi of the two hemispheres. In addition, fibers from the mammillary body can be traced via a conspicuous bundle, the tract of Vicq d'Azyr, to the anterior thalamic nuclei—the origin (*vide infra*) of the projections to the cingulate cortex.[36]

Summary. From observation in normal stained material of the connections of the allocortical and juxtallocortical formations, three interconnected "systems" can be discerned. The first consists of primary olfactory structures apparently directly related to the olfactory bulb.* The second receives fibers from the first and consists primarily of the septal region and the amygdaloid complex. The third "system" consists of cingulate and entorhinal cortex and the structures of Ammon's formation. These appear to be remotely, if at all, related to olfactory afferents. (See excellent review by Brodal.[27]) Both the second and third "systems" send efferents to the hypothalamus.

Axonography of normal material thus supports the morphological distinction between those allo- and juxtallocortical areas related to the first and second system (semi- or paleocortical) and those related to third system (archicortical) formations. The distinction between first and second systems on the basis of direct connections with the olfactory bulb would prove useful if substantiated by more reliable techniques, since one of the referents of this review is "olfactory" function. We proceed, therefore, to an examination of experimental anatomical material.

C. *Experimental Histology*

In many instances, more specific information regarding the interrelationships of these several morphological units has been derived from experimental material. Four staining methods have been employed in tracing the course and termination of fibers originating at the site of an experimental lesion of the brain: the Weigert technique uses hematoxylin to trace neural pathways by their myelin content (interrupted pathways lose their myelin and fail to stain); the Marchi technique employs osmic acid to trace granules of degenerating myelin along interrupted pathways; the Bielshowsky silver method has recently been modified to demonstrate the dissolution of nerve fibers; and modifications of Nissl's thionin or methylene blue stain for cell bodies have been used to show gliosis along degenerating pathways or in related nuclei, and to determine the loss of cells in a structure due to retrograde degeneration when most of the fibers are severed from a parent cell. Each of these techniques has limitations; on the whole, however, those studies employing Nissl stain to study retrograde degeneration and those restricted to *terminal degeneration* when the silver stain is used, are the most reliable. The latter, however, may also demonstrate connections which are sparse.

Following lesions of the olfactory bulb (or, in monkey, of the tract emerging from the bulb), degenerating fibers may be traced in the rostral part of the anterior commissure to the bulb on the opposite side.[32, 39, 49, 105, 124, 166] Such lesions also result in degenerating fibers reaching the olfactory tubercle and, via the medial olfactory tract, the anterior portion of the supracallosal hippocampal rudiment. In addition, degenerating fibers can be traced to the prepyriform area, and the periamygdaloid cortex.[39, 105] Johnston[75] had divided this complex into corticomedial and basolateral groups on a comparative morphological basis. Only the corticomedial group receives direct fibers from the olfactory bulb.

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* In this review, the olfactory bulb is considered analogous to the thalamus. Both bulb and dorsal thalamus [see Rose and Woolsey[131] for review] contain structures which receive the final terminals of afferents from sense organs before relay to cerebral cortex. Thus, the numbering of our system proceeds from the bulb.

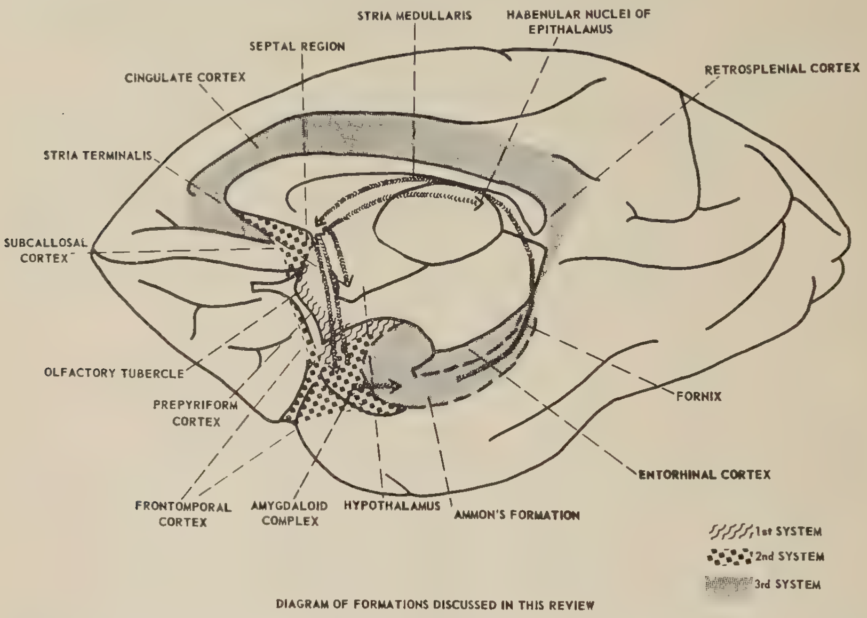

FIGURE 1. Diagrammatic representation of the mediobasal surface of a monkey brain outlining the formations discussed in this review and their relationships.

Discrete destructions separating those parts of the amygdaloid complex which receive olfactory afferents from those receiving none have not been accomplished. However, some information regarding connections can be gained from lesions limited to periamygdaloid cortex,[155] others including the entire amygdaloid complex,[47] and still others involving the stria terminalis.[49] Periamygdaloid cortex sends fibers to at least some portions of the frontotemporal juxtallocortex and to the basolateral amygdaloid nuclei,[13] which, in turn, give rise to the major portion of the stria terminalis (the latter also includes fibers from the bed nucleus of the stria, a part of the corticomedial group). In these experiments the fibers of the stria terminalis can be traced to the septal region. Components of the anterior commissure are also found degenerated following amygdala lesions and can be traced to the amygdaloid complex of the opposite side.[47] Finally, fibers can be traced from lesions of the amygdaloid complex (especially the basolateral group) to the ventromedial nucleus of the anterior hypothalamus.[2]

We turn to the interconnections of the third system as demonstrated by the methods of experimental anatomy. Whereas lesions of the amygdaloid complex do *not* result in degenerating fibers reaching the entorhinal cortex,[13] those of entorhinal[12] and cingulate cortex[1,3] give rise to degenerating fibers which can be traced to Ammon's formation. Experimental evidence confirms the findings based on normal material that the fornix serves as the major efferent from this formation to the rest of the nervous system.[11,57,141,147] Simpson's[141] study divides the fornix into two divisions, a precommissural and a postcommissural. The former, and several times larger by fiber count, terminates in the septal region; the latter, in the mammillary body. Furthermore, when lesions are restricted to the anterior part of Ammon's formation, degenerating fibers can be traced only to the septal region[82,119] although an abnormal number of boutons terminaux appear in the mammillary nuclei;[141] lesions involving the posterior portion of Ammon's formation result in fiber degeneration which extends to the mammillary body.[109,141] Degenerated fibers from lesions in the septal region have also been traced to the mammillary body.[113] By means of the Marchi method, some fibers are reported to course back in the dorsal fornix to Ammon's formation.[57] It is, however, somewhat difficult to ascertain the directionality of the degenerating fibers with this method.

From lesions of the mammillary body, Le Gros Clark[36,38] traced fibers to the anterior nuclei of the thalamus. These, in turn, project to the cingulate cortex[22,120,130,160,161] which, as we have already seen, is the origin of some of the fibers to Ammon's formation.

Another "circuit" has recently come to light. As mentioned above, the stria terminalis connects the amygdaloid complex and the septal nuclei with the anterior hypothalamus. This, in turn, sends fibers to the midline and intralaminar nuclei of the thalamus.[37,110] Silver techniques have shown these thalamic nuclei to project to the prepyriform, subcallosal, cingulate and entorhinal cortices which provide afferents to Ammon's formation.[114] These findings were anticipated by the results of several studies utilizing the retrograde degeneration in the thalamus which follows cortical resections.[14,119,131]

Recently still another experimental technique has been applied to the olfactory system by Bodian.[23] Extensive studies had shown that the spread of poliomyelitis virus within the nervous system conforms to known neural pathways. After inoculation of the olfactory mucosa, poliomyelitic lesions were found in the (1) bulb, (2) olfactory tubercle, (3) nucleus of the diagonal band, (4) prepyriform cortex, and (5) corticomedial group of the amygdaloid complex. In addition, some degeneration was found in the hypothalamus, the inferior claustrum, midline thalamic and habenular nuclei, and globus pallidus. No lesions were found in Ammon's formation, mammillary nuclei, putamen, caudate nucleus, or lateral thalamus. On the other hand, injection of the fornix causes extensive destruction in Ammon's formation. Thus the relatively direct connection between olfactory receptor and the first system is again validated; the lack of such connections with the third system is again emphasized.

Summary. (See Figure 1.) On the basis of experimental anatomical studies, a more definitive description of the primary olfactory system may be given: from the olfactory bulb (either directly or via the anterior olfactory nuclei), olfactory afferents reach medially to the olfactory tubercle, the anterior extremity of the supracallosal hippocampal rudiment, and laterally to the prepyriform and periamygdaloid cortex. Direct connections from the bulb could *not* be traced to any other structures discussed heretofore: specifically, *no* olfactory afferents reached the septal nuclei, the basolateral group of the amygdaloid complex, the entorhinal and cingulate cortex or Ammon's formation. Thus a clearer picture of the *second* system emerges from the experimental studies as compared with that obtained from normal material: the frontotemporal (and possibly the subcallosal) juxtallocortex, the basolateral group of the amygdaloid complex, and septal nuclei are now included. In keeping with the semicortical classification of this system, parts of it are cortical, parts form subcortical nuclei.

The impressions concerning the organization of the third system derived from normal anatomy are verified and considerably amplified by experimental studies. This system centers around Ammon's formation, which receives fibers from the entorhinal and cingulate cortex. The main efferent path of Ammon's formation, the fornix, projects to the septal nuclei and to the mammillary body of the posterior hypothalamus. The septal nuclei also send fibers to the mammillary body, and both septal and amygdaloid complexes project to the anterior hypothalamus via the stria terminalis. From anterior and posterior hypothalamus, pathways have been traced via anterior and midline thalamus to prepyriform, entorhinal, and cingulate cortex. Thus, multiple closed loops characterize the connections of the third system; these involve the structures of the second system and those of the hypothalamus as well as those of the anterior and midline dorsal thalamus.

D. Electrographic Anatomy

The histological techniques discussed so far are applied to the study of the brain *in vitro*. Since the development of electrical stimulation, amplification, and recording devices, pathways may also be traced in the living animal. Another method for checking the relationships of neural structures is thus available.

When the olfactory apparatus is exposed to stimulants (*e.g.*, guiacol, cloves, asafetida, indol, chinolin, or smoke), changes can be observed in the electrical activity in the region of the olfactory bulb and tract, olfactory tubercle, septal region, prepyriform and periamygdaloid cortex, and the Ammon's formation.[4, 10, 63, 100] Because of technical difficulties, stimulus control has been crude; in addition, systematic mapping of responsive and nonresponsive points has not yet been done. Thus the results are tentative, but they indicate that many of the structures included in each of the three systems may be excited by stimulation of the olfactory apparatus. Precise data are more easily obtained from experiments utilizing electrical stimulation of neural structures. As the olfactory fila are difficult to explore in most mammals, the olfactory bulb has been the choice of most investigators using this technique.

TABLE 2

SUMMARY OF ELECTROGRAPHIC RESPONSES TO OLFACTORY BULB STIMULATION

Neural formation	*Rose & Woolsey* (129)	*Fox, et al.* (48)	*Kaada* (77)	*Berry, et al.* (19)
Olfactory tract	+	+	+	+
Olfactory tubercle	0	+	+	+
Diagonal band	0	0	—	+
Septal region	—	0	0*	+
Prepyriform cortex	+	+	+	+
Periamygdaloid cortex	+	+	+	+
Basolateral amygdaloid nuclei	—	0	+	+
Frontotemporal cortex	—	—	+	—
Anterior entorhinal area	+ (small)	—	+** (inconsistent)	+
Retrosplenial area	0	—	—	+
Cingulate cortex	—	—	0	+
Ammon's formation	0	0	0*	+
Caudate (head)	—	—	—	+
Putamen	—	+	—	+
Globus pallidus	—	+	—	+
Claustrum	—	-	—	+

*Present under chloralose anesthesia
**In posterior portion: only under chloralose anesthesia

+ = Response
0 = No Response
– = Not Reported

Electrical stimulation of the olfactory bulb results in abrupt changes in the electrical potential recorded from presumably related structures. Using the conventional techniques of recording with a large exploring electrode, all of the structures which have been classified on an experimental anatomical basis as belonging to the first system have been shown to be activated by bulb stimulation in at least two independent studies, although discrepancies exist (see TABLE 2). All of these structures respond with sufficiently short latency to preclude the probability of multisynaptic connection and can, therefore, be designated as "primary."

With regard to the second and third systems as defined on the basis of anatomical data, the results of electrical studies are less clear. All of the investigations using a conventional electrode have produced negative results, except for some scanty observations using chloralose anesthesia.[77] However, Berry *et al.*,[19] using small (50 micra) bipolar electrodes, which by virtue of their size might be expected to record potentials from only a few elements, have been able to record potentials from some of the structures which have been designated as second and third systems on histological grounds. Differences in latencies distinguish the response in different systems: structures in the first system respond within 4 msec.; in the second system, within 10 msec.; and, in the third, at widely varying intervals longer than 10 msec. For example, the prepyriform cortex yields a response

1.2-3.0 msec. after bulb stimulation, the response from the periamygdaloid cortex is obtained at 2.5-4 msec., whereas the responses from Ammon's formation were found after latencies of 10-32 msec. and those near the mammillothalamic tract after 25-34 msec. Responses also appeared in the frontotemporal juxtallocortex and parts of the striatum, supporting prior findings of comparative anatomists.[64, 75]

Electrical stimuli have also been applied to structures included in the third system, and the resultant electrical activity in other neural structures have been investigated. Essentially, these experiments confirm the previously outlined interrelationships within this system. Thus, Renshaw *et al.*[125] showed that the hippocampus is activated by entorhinal stimulation; both an afferent and efferent relationship between Ammon's formation and the septal region via the fornix has been found;[52] and the posterior cingulate cortex was activated by stimulation of the mammillary body.[164]

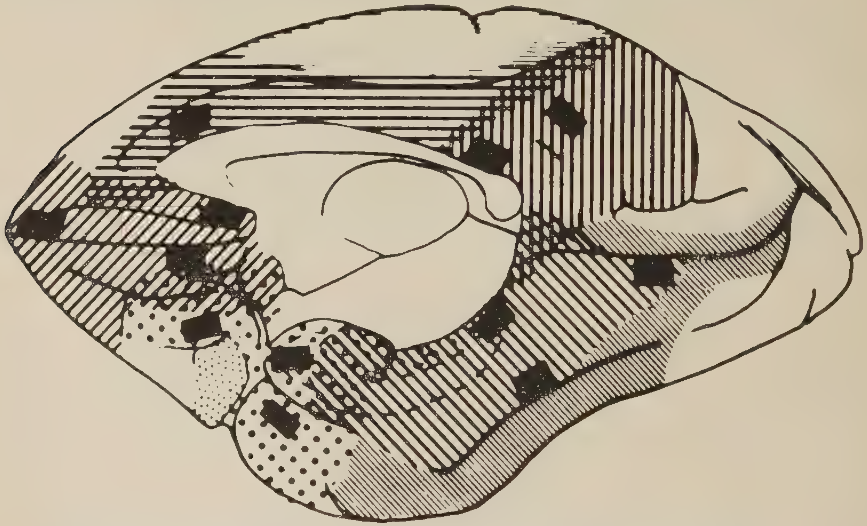

FIGURE 2. Diagrammatic representation of the mediobasal surface of a monkey brain showing the distribution of neuronographically determined subdivisions. Black rectangles indicate representative sites of strychninizations: hilar sites of allo- and juxtallocortex, more peripheral ones of isocortex. Coarse stippling or striations indicate regional parcellations based on reciprocally related cortical points. Finer stippling or striations represent maximum additional cortex unidirectionally activated from within a region. Taken from Pribram and MacLean.[122]

A further check of these relationships comes from the changes in electrical potentials induced by chemical stimulation of neural structures, usually by the local application of strychnine. Such "neuronographic" studies (FIGURE 2), in addition to confirming most of the findings discussed above, substantiate the relation, proposed on the basis of anatomy, of much of the mediobasal cortex with Ammon's formation.[101, 121, 122, 152] These studies support the conception that, in spite of the increased development which the juxtallocortex shares with isocortex in primates, juxtallocortical areas are better classified with the particular allocortical formations to which they are related.

Summary. In reviewing the electrographic data, therefore, one finds an independent method which supports the conceptions derived from ontogenetic, normal, and experimental anatomy. Allo- and juxtallocortical formations may be grouped into three systems. The first system consists of olfactory tubercle, area of the diagonal band, prepyriform cortex, and the cortico-medial nuclei of the amygdala. This system has direct connections with the olfactory bulb. A second system has only secondary connections with the olfactory bulb. It consists of the basolateral nuclei of the amygdala, the septal nuclei, the frontotemporal (and possibly the subcallosal) juxtallocortex, and probably includes basal parts of the striatum. On histogenetic grounds, the structures grouped as first and second system (semicortex and perisemicortex) were distinguished from Ammon's formation and related cortex (archicortex and periarchicortex). This distinction is supported by axonography. The third allo- and juxtallocortical system composed of Ammon's formation and cingulate and entorhinal cortex has abundantly demonstrated electrographic as well as histological intraconnections and is only remotely related by any technique to the olfactory bulb.

Discussion

Because of recent interest in the possible role in emotional behavior of parts of the forebrain which previously had been thought to serve olfaction, we have reviewed observations and experiments concerning the anatomy of the "olfactory brain" or "rhinencephalon." We have chosen to include all morphological formations not typically isocortical; *i.e.*, those which do not definitely pass through a six-layered stage in ontogeny. This choice has been determined by two considerations. Speculation has included transitional (juxtallocortical) formations as well as allocortical ones in the neural substrate of emotion; data can be more simply organized when both allo- and juxtallocortical formations are included. In mammals, and especially primates, the increase in isocortical relative to allocortical formations is shared by the increased development of the juxtallocortical ones. Thus the classical distinction between neocortical and older formations is modified in favor of the distinction between isocortex on the one hand and allo- and juxtallocortex on the other. In addition, the classical distinction between paleo- and archicortex is broadened to include the transitional formations related to each type of allocortex (semi- and perisemicortex on the one hand; archi- and periarchicortex, on the other). The histogenetic evidence upon which these distinctions are based has been reviewed.

Lorente de Nó[96] has pointed out the limitation of all cytoarchitectonic classifications based on Nissl preparations. Essentially, his criticism is that differences which appear between cortical areas in Nissl preparations do not appear when other staining methods are used. Such criticism implies that the cerebral cortex may be subdivided in only one way which can be specified by the application of a variety of anatomical techniques. An alternative conception would consider that different methods of subdivision are possible, each delineated by one of several techniques and each correlating with different functions. One cortical area might thus be part of two differently organized cerebral systems. In this frame of reference, different anatomical techniques might be expected to uncover different principles of cerebral organization. The relevance of *each* principle to function would have to be established separately. A static conception of "the" function of a cerebral area is replaced by a dynamic conception which considers the different functions of an area under different conditions. The conditions examined in this review are those leading to olfactory and emotional behavior; the relevance to such behavior of the morphological distinctions outlined rather than their *anatomical* generality is in question. Nevertheless, support for the acceptance of the classification based on histogenetic data has come from a review of the interrelationships between the several morphological units included under allo- and juxtallocortex. An additional distinction could be made between those structures receiving axons from the olfactory bulb and those which do not. Thus, on the basis of connections, three systems were described; the distinction between the second and third supporting a similar distinction based on histogenesis.* The three systems are defined as follows: the first, or primary system, receives afferents from the olfactory bulb; the second and third do not. The second system is defined in terms of direct connections with the primary; the third system has no such connections, but is connected with the second. As primary system we have included the olfactory tubercle, area of the diagonal band, prepyriform cortex, and the corticomedial nuclei of the amygdaloid complex. The main components of the second system are not all cortical; they include the subcallosal and frontotemporal juxtallocortex, the basolateral nuclei of the amygdaloid complex, and the septal nuclei; in addition, there is evidence that at least portions of the striatum ("olfactory" striatum) should be included, evidence which is in congruence with the semicortical ontogeny of this system. The third system centers around Ammon's formation; it includes also the entorhinal, cingulate, and retrosplenial juxtallocortical areas.

The major interrelationships between the three systems may be described as follows: beginning at the olfactory bulb, fibers can be traced to a *primary* olfactory system consisting of olfactory tubercle, olfactory trigone, the prepyriform cortex, and the corticomedial nucleus of the amygdaloid complex. The primary system of each hemisphere is connected to that of the opposite hemisphere by the rostral fibers of the anterior commissure. This system is connected with the subcallosal and frontotemporal cortex and through the medial and lateral striae with the septal nuclei, nuclei of the diagonal band, and the basolateral part of the amygdaloid complex. These structures make up the second system interconnected through the anterior commissure and stria terminalis. As noted, some comparative studies and electrographic data suggest that parts of the striatum might profitably be included in this system. Efferents from the septal nuclei and amygdaloid complex reach the epithalamus and anterior hypothalamus; in turn, the latter connects with the midline and intralaminar nuclei of the dorsal thalamus. These nuclei apparently project to the juxtallocortex. Ammon's formation receives fibers from the cingulate, retrosplenial, and entorhinal part of this cortex, thus making up the third system. This system, in addition to the circuit involving *anterior* hypothalamus via the fornix and the septal nuclei, is also related to the *posterior* hypothalamus (mammillary bodies) via the fornix. The mammillothalamic tract, and the projections from the anterior thalamic nuclei to the cingulate juxtallocortex, and the fibers to Ammon's formation from the cingulate cortex complete the circuit.

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* Actually, the distinction between first and second system can also be made on a histogenetic basis: the first system is semicortical; the second, perisemicortical and subcortical. However, a similar distinction between archi- and periarchicortical formations was not made on the basis of axonography. (It could have been, if a more complex definition had been invoked.) Thus, whether allo- and juxtallocortical formations are grouped into three or four systems is arbitrary.

Table 3

Summary Systematization of Rhinencephalic Formations

System	*Definition*	*Morphological Formations Included*
First	Direct connections with olfactory bulb	Olfactory tubercle; area of diagonal band; prepyriform cortex; corticomedial nuclei of the amygdaloid complex
Second	Direct connections with first system but none with bulb	Subcallosal and frontotemporal juxtallocortex; septal nuclei and basolateral nuclei of the amygdaloid complex
Third	Direct connections with second system but none with bulb or first system	Ammon's formation; entorhinal, retrosplenial, and cingulate juxtallocortex

Summary. A definition of "rhinencephalon" which includes juxtallocortical as well as allocortical formations was chosen because of recent interest in the possible functions of these portions of the brain in emotional as well as olfactory behavior. This choice has proved useful in subsuming a large body of data derived from the application of phylogenetic, ontogenetic, axonographic, and electrographic data. This definition of "rhinencephalon" modifies the classical distinction between neocortical and older formations in favor of a distinction between isocortex on the one hand and allo- and juxtallocortex on the other. Findings have been reviewed which support the classification of "rhinencephalic" structures as thus defined into three systems (see TABLE 3). The distinction between the first and second systems on the one hand and the third system on the other are extensions of the phylogenetic distinction between paleo- and archicortical formations. This distinction is supported by histogenetic, axonographic, and electrographic data. The distinction between the first and second systems is most reliably rooted in experimental histological studies. The inclusion of subcortical as well as cortical formations in the second system is derived as well from phylogenetic, ontogenetic, axonographic, or electrographic techniques. Each system is abundantly intraconnected. Both second and third systems are efferently related to the hypothalamus and afferently related to the anterior and midline thalamus. These intra- and interconnections provide the anatomical base for a consideration of the functions of these systems which follows.

III. FUNCTIONS OF "RHINENCEPHALIC" SYSTEMS

A. Experimental Physiology

We now turn from investigations concerning the organization of the "olfactory brain" to investigations of function. As already noted, changes in electrical potential can be recorded in many of the formations considered in this review when the olfactory apparatus is exposed to stimulants. The initiation of such changes is not limited to "olfactory" stimulation, however. MacLean *et al.* have shown that, in the prepyriform, periamygdaloid, and entorhinal cortex, in the basolateral amygdaloid nuclei, and in Ammon's formation, such changes may also be produced by placing salt on the animal's tongue or pinching its tail and extremities.[100] There is some additional though scanty evidence[56,127] that tactile, auditory, and visual stimuli affect the electrical activity of the third system (specifically Ammon's formation and the cingulate gyrus); it is thus likely that, while the several morphological formations included in this review have been shown to be influenced by olfactory stimuli, they are influenced, as well, by "nonolfactory" stimuli.

Such experiments delineating the afferent physiological control of the structures reviewed have been few. On the other hand, recent observations of the efferent control this system exerts on effectors have been many. Numerous investigators have electrically and chemically stimulated the various morphological formations under consideration.[54,86,93,126,144] Some of the effects of such stimulation might have been predicted on the basis of the respiratory and vascular responses which follow inhalation of various odoriferous gases.[5,6,20,85] In addition, gross movements apparently not somatotopically localized have been described repeatedly and have been reviewed by Kaada[77] and Gastaut.[55] Such effects have been systematically studied. Stimulation of every structure included in the first and second systems as well as the anterior portions of the third (bulb, tract, tubercle, diagonal band, septal region, prepyriform cortex, amygdaloid complex, and frontotemporal, subcallosal, and anterior cingulate regions) has resulted in respiratory, vascular, and gross motor changes.[78] In addition, respiratory and vascular responses have been found on electrical stimulation of the habenula and anterior and midline thalamic nuclei, but not elsewhere in the thalamus.[138] Similar effects from Ammon's formation are more readily demonstrated by chemical (sodium citrate) stimulation.[7] The characteristics of these responses have recently been reviewed by Kaada[77] and Gastaut.[55] In this presentation it is sufficient to point out that in view of other efferent as well as afferent relationships most allo- and juxtallocortical formations cannot be solely designated as olfactory. Recently the control of visceral function (through the autonomic nervous system) by these formations has been promulgated and other relationships neglected. In the light of the efferent control of somatic movement exerted by allocortex and juxtallocortex and, conversely, the control of the autonomic nervous system exerted by the lateral isocortex,[65,89,118,137,159] it seems preferable to emphasize the massive and diffuse nature of the allo- and juxtallocortical control of both smooth and striped muscle (as contrasted with the more discrete control exerted by the lateral isocortex).

With respect to delineation of a specific function for allocortical and related systems, another electrophysiological finding is of interest: electrical stimulation of many of these formations results in a spread of altered electrical activity to the other related formations (prolonged after-discharge, activation and depression of spontaneous rhythms, and abolition of strychnine spikes and burst potentials) and, under certain conditions, to the rest of the cerebrum as well.[76,77,89,90,125] These phenomena could possibly be mediated via the midline and intralaminary nuclei from which "recruiting" responses are obtained.[41,51,69,70,71,111,151] It is more likely that interaction between midline-intralaminar and anterior thalamic nuclei, the cortex to which they project (prepyriform, subcallosal, frontotemporal, cingulate, and entorhinal), and Ammon's formation provides the basis for such generalized changes in cerebral electrical activity. Another related finding of great interest is that peripheral stimulation which "arouses" the animal and "activates" the electrical activity of the isocortex[50,51,52,69,70,71,91,92,102,103,112,117,148,149,150] apparently results in electrical hypersynchrony in Ammon's formation.[59]

Summary. Physiological experiments support the conception that the allo- and juxtallocortical formations have different functions from typically isocortical formations. These experiments emphasize the diffuse nature of the relationships between allo- and juxtallocortical formations and peripheral structures, confirming Herrick's earlier findings utilizing phylogenetic material.[64] There appears to be no basis for the substitution of "visceral" for "rhinal" in designating the functions of most of these formations; both terms suggest a particular selective function common to all formations included in this part of the brain which is not supported by evidence. (See discussion of MacLean by Pribram.[98]) On the other hand, the diffuseness of the relationships of these formations with peripheral structures contrasts sharply with the discreteness of the organization of afferent and efferent projection systems to parts of the isocortex. This difference may prove to be fundamental.

B. *Experimental Psychology*

There remains to be considered another type of evidence regarding the functions of the "rhinencephalon": studies of the behavior of the animal following excision or stimulation of neural structures. Can the three systems delineated by anatomical and physiological techniques be distinguished on the basis of their relation to olfactory or emotional behavior? Is such a relationship, if demonstrated, a selective one? These questions cannot yet be answered fully because of the paucity of available data. However, a beginning has been made, and these experiments are reviewed.

Extensive and clearcut experiments on olfactory discriminations were performed by Swann.[153,154] Using 130 rats trained in a T maze in which odorous wood shavings were placed on one side, he found that olfactory bulb excision and section of the intermediate olfactory stria impaired discrimination. Sections of the (1) medial and (2) lateral olfactory stria, and (3) lesions of the septal region, (4) prepyriform cortex, (5) amygdaloid complex, and (6) Ammon's formation failed to interfere with performance. Neither small isocortical lesions nor extensive ones involving as much as 85 per cent of the total cortex interfered with performance. Additional experiments by Brown and Ghiselli[30] failed to confirm Swann on the effects of sections of the intermediate olfactory stria and, in addition, showed that extensive lesions of many subcortical masses also failed to interfere with such discriminations. The only structures classified as "olfactory brain" by anatomists which were not involved in these experiments were studied by Lashley and Sperry.[88] In these experiments, the radiations from the anterior nuclei of the thalamus to the cingulate cortex were interrupted, and time for retrograde degeneration was allowed to elapse. Again, no alteration in discrimination performance resulted. It seems, therefore, that, with respect to the most elementary behavior determined by olfactory cues, only the olfactory bulb has been shown to be significant.

A somewhat more complicated olfactory discrimination utilizing the conditioned foreleg response of dogs was used by Allen.[8,9] He found that lesions of pyriform cortex and amygdaloid complex and the associated frontotemporal cortex resulted in the loss of a "negative" conditioned habit (though the "positive" was retained). In other words, animals which had been trained (using aversive stimulation) to raise the foreleg whenever cloves were presented and to refrain from raising the leg when asafetida was used as stimulus, after surgery, raised the foreleg to both cues. Ablation of Ammon's formation failed to alter preoperative performance. None of these lesions affected the ability of a blindfolded dog to pick out a bag containing meat from others containing sawdust. These results essentially confirm those of Swann; the loss of the "negative" conditioned response may be due either to a *selective* loss of ability to discriminate between several olfactory cues or to a more *general* change affecting either the reaction to aversive stimulation or a whole range of complex discriminations.

Because of the difficulties in separating introspectively the sensations of smell and taste, and the occurrence of "uncinate" seizures in man which sometimes include both, it has been suggested that the amygdaloid complex and Ammon's formation are concerned in gustatory as well as olfactory functions. We have already seen that gustatory stimulation will alter the electrical activity of these structures. Quantitative tests of monkeys' preference for water over a bitter quinine solution show, however, that the insular-opercular cortex rather than the amygdaloid complex or Ammon's formation are implicated in "primary" gustatory functions.[14,21] On the other hand, a change in dietary habits is observed following ablations of the amygdaloid complex and surrounding cortex,[119] an effect *not* obtained from lesions elsewhere (either in the insular-opercular, Ammon's, or lateral isocortical formations). These changes in gustatory behavior following amygdala resections, may be explained, as in the case of olfaction, in one of two ways: (1) the animal may be unable to *select* between several cues whether these are olfactory or gustatory and the change is limited to these modalities, or (2) the animal may be more *generally* impaired with respect to any complex discrimination. The latter interpretation is untenable in the light of a considerable body of experimental evidence. Resections limited to the second system fail to interfere with learned visual discriminations [119] or with performance of such tasks as delayed response and delayed alternation.[119] These findings take on added significance from the fact that isocortical ablations adjacent to the second allo- and juxtallocortical system markedly impair an animal's performance of these tasks.[108, 109, 123]

However, disturbance is not limited to olfactory and gustatory behavior when the second system is stimulated or extirpated. Changes in temperature regulation, in quantity of food intake, and in sleep-activity cycles have been reported.[119] While one is tempted to look for some phrase which subsumes all of these categories of behavior, it is probably best to wait for additional evidence before making the attempt. The advisability of waiting is emphasized by yet another series of disturbances in behavior which follow lesions of allo- and juxtallocortex; *i.e.*, disturbances of "emotional" behavior.

Following the almost simultaneous publication of the effects of resection of the entire temporal lobe of monkeys (including the amygdaloid and Ammon's formations) by Klüver and Bucy [81, 82, 83] and the theoretical inferences derived from anatomy about "emotional behavior" by Papez,[116] a number of investigators have become interested in this problem. Klüver and Bucy, confirming an older report by Brown and Schäfer,[31] found, amongst other effects, that temporal lobectomy resulted in marked taming of monkeys. Papez suggested that the circuit nature of Ammon's formation, fornix, mammillary body, anterior thalamic nucleus, cingulate cortex, Ammon's formation, constitutes an anatomical base for emotional behavior. Experiments by Smith [143] and Ward,[162] in which the anterior cingulate gyrus was resected with effects on general behavior similar to those described by Klüver and Bucy, tended to support the Papez hypothesis.

Another series of experiments, motivated by considerations other than those described above, have implicated the anterior rhinencephalic structures (especially of carnivores) in "emotional" behavior. Spiegel *et al.*[146] in acute preparations showed that the "rage reactions" observed previously in decorticated cats[17] and after prechiasmal incisions[53] could be obtained from lesions in the region of the olfactory tubercle and amygdaloid complex. In an extensive series of chronically observed cats, Bard and Mountcastle [16] showed that ablation of the entire isocortical mantle failed to produce such symptoms; in fact, such cats became refractory to most stimulation. If additional damage was inflicted on either the midline (cingulate) cortex or to the region of the amygdaloid complex, the animal's threshold of excitation dropped markedly and "rage reactions" were displayed. When isocortex was uninjured, such reactions resulted only from ablations of the region of the amygdaloid complex—though, in many instances, only after a delay of several weeks. Removal of Ammon's formation resulted in a more "placid" animal. More recently Schreiner *et al.*[139] reported another series of carnivores in which extirpations in the region of the amygdaloid complex had been made. Contrary to Bard and Mountcastle, these authors found a marked diminution of "aggressive" behavior following such lesions. These latter results are in consonance with those obtained in primates; however, until adequate comparison of the precise locus of lesions is possible and until the postoperative environmental variables are controlled, no definitive statement resolving this discrepancy is possible. Nevertheless, irrespective of the direction of change, all studies agree that the dimension of change is "emotional" behavior.

Corroboration for some of the alterations observed to follow ablations of these structures comes from electrical and chemical stimulation. "Arrest," "avoidance," and "attack" may be provoked by such stimulation of the amygdaloid complex in the unanesthetized animal.[55, 99] In addition, ablation experiments in the immediate past have supported the findings that the structures classified as the second system (frontotemporal juxtallocortex, amygdaloid complex, and septal region) are implicated in "emotional" behavior.[25, 54, 113, 145, 163]

In some of these experiments, social [135] and other [25, 163] environmental conditions have been rigorously controlled and the anatomical effect of surgery carefully specified. One series of such experiments demonstrated that behavior based on "fear" as measured by a conditioned avoidance response is especially disturbed by lesions of the frontotemporal cortex and amygdaloid complex. This finding, taken together with previously reviewed evidence, confirms the impression obtained from studies involving olfactory and gustatory behavior as well as those involving energy relationships (food intake, sleep, activity, and temperature regulation) that the second system serves a variety of functions which, thus far at least, cannot be easily subsumed under any "primary" category.

The major portion of the hypothesis of Papez has not fared as well in gaining adequate experimental support. Although promulgated and amplified in an excellent review by MacLean,[97] exploration of the effects of stimulation and resection of the supposed anatomical substrate of emotion have thus far been few and crude. The experiments of Smith and Ward concerning the effects of cingulate ablations have not been confirmed. Since neither Smith nor Ward presented anatomical verification of their lesions, or explored behavior by any systematic techniques, subsequent findings [58, 120] must be considered. In addition, as already mentioned, systematic analysis [21, 34, 35, 108, 109, 119, 135, 163] of the syndrome reported by Klüver and Bucy has thus far related the "emotional" and "social" changes in behavior following temporal lobectomy to involvement of the region of the amygdaloid complex. Studies from other laboratories[25,156,158] confirm these findings and extend them to include the effects of lesions of the septal nuclei.[113] Thus, at present, an abundance of evidence implicates the second rather than the third system in emotional and social behavior whereas evidence with respect to the functions of the third system remains sparse. A few stimulation studies[67,99] indicate that arrest of ongoing behavior sometimes results. These observations, however, are still fragmentary. Often seizure discharges can be recorded from Ammon's formation in the absence of any observable changes in an animal's behavior. We must face the fact that up to now there have been no reliable clues from behavioral studies as to the function of the third system.

Summary. The results of experiments utilizing behavioral techniques may be summarized as follows: Only the olfactory bulb has been implicated in simple olfactory discriminations. It is possible that resections of the primary system were not complete enough to result in olfactory discrimination deficits, since it has been found that, in vision,[62,140] somesthesis,[136,167,168,169] audition,[42,44,73,104] and gustation,[14] removals of primary projection cortex must include practically the entire system before any discrimination deficit results.

Deficits in olfactory discriminations utilizing "negative" responses have, however, been reported to follow ablations in the region of the amygdaloid complex. Similar changes with respect to gustatory discriminations follows such lesions. These changes are not *generalized* to visual behavior nor do they extend to such tasks as delayed response. However, the effect of amygdala lesions is not *restricted* to olfactory-gustatory behavior. Changes in regulation of quantity of food intake, temperature regulation, and sleep-activity cycles occur. Furthermore, lesions anywhere in the second system (amygdaloid complex, septal region, and frontotemporal and subcallosal juxtallocortex) affect emotional behavior (*e.g.*, as measured by conditioned avoidance responses). It seems, therefore, premature to speculate regarding the "essential" function of the second system.

The third system has remained recalcitrant to date. Behavioral investigations have thus far been too crude and sparse to support Papez' much publicized speculations regarding the neural substrate of emotion.

Discussion

Studies of function have so far implicated only the olfactory bulb in simple olfactory discriminations. This may be due in part to difficulty in making total removals of the primary system, which is spread out along the length of the olfactory striae. A working hypothesis (based on anatomical knowledge of the connections of the primary olfactory system and the neuropsychological data obtained for the primary projection systems in vision, gustation, and somesthesis) would predict olfactory discrimination deficits to follow only when the greater portion of cortex which receives direct afferents from the olfactory bulb is removed. This hypothesis is testable with available surgical-anatomical and behavioral techniques provided a macrosmatic species is used.

A profusion of changes in an organism's behavior follows resections or stimulations of the second system. The following three formulations of these effects are possible:

(1) A simple hypothesis may be suggested to account for the variety of changes. It is possible that the second system as defined in this review must be further subdivided and that a separate function may ultimately be ascribed to each subdivision. If this is the case, the syndrome which follows lesions of the second system could be analyzed into components by selective ablations.

(2) On the other hand, the observed changes in olfactory-gustatory behavior (not simple preference threshold changes) *might* be related to changes in quantitative food intake, sleep-activity cycles, and basal temperature. These, in turn, *might* be related to the changes in "emotional" behavior as measured by the change in social reactions and in conditioned avoidance responses. At present, data are insufficient to formulate such a relationship in precise terms. Imprecisely, this hypothesis would consider one basic change in the organism's reaction to its environment to underlie the various manifestations. The changes in behavior following lesions of the second system are reminiscent of those following hypothalamic lesions; however, they are less drastic. Whereas an animal with hypothalamic damage will be either unreactive or become abruptly and vigorously hyperreactive to environmental change, the animal with lesions in the second allo- and juxtallocortical system will be hypo- or hyperactive within the limits of apparently adaptive and thus less "abnormal" behavior. It has often been stated that the key to understanding the cerebral isocortex lies in the dorsal thalamus; in a similar manner, the key to understanding the second allo- and juxtallocortical system may be found in the hypothalamus. As was pointed out, these changes in behavior cannot be ascribed solely to the relationship of hypothalamus and second system with autonomic and visceral mechanisms. There is no evidence of a *selective* afferent or efferent relationship between the autonomic nervous system and allo- and juxtallocortical formations. As is the case with stimulation of the hypothalamus, the massive autonomic discharge which follows excitation of many of the structures of the second system has obscured the equally massive mobilization of the somatic motor system which frequently occurs, especially in unanesthetized animals. The current obfuscation derives in part from the effects on emotional behavior produced by such stimulation; the acceptance of "visceral" theories of emotion, such as those of James [68] and Lange;[87] and the still older conceptualization of the basis of "feeling" which are carried in our everyday language.

(3) A third hypothesis concerning the variety of effects which follow resections and stimulations of the second system must be considered. It is possible that the second system (as well as the hypothalamus) serves several functions, not because it is composed of several subdivisions, each of which

is related to some separate function, but because the second system may, in the living organism, become a part of several larger systems. For example, it is possible that the olfactory-gustatory functions of the second system depend on the relationship between it and the primary olfactory and primary gustatory projections. The metabolic functions of the system may, on the other hand, depend on the relationship of the second system to the hypothalamus. Finally, the changes in socio-emotional behavior may be the result of interference with the interrelationship between the second system and the frontal isocortex. This hypothesis is based on a principle of cerebral organization other than the classical static one derived exclusively from the organization of the peripheral nervous system. Such a principle, that of "dynamic" organization, was proposed earlier in this review in a discussion of the criticisms of histogenetic data.

It seems fruitful to pursue investigations designed to test any of the hypotheses concerning the functions of the second system. At present there seems to be no basis for choosing one hypothesis rather than another except by personal preference which depends, in part, on the investigator's relative facility with anatomical, electrophysiological, surgical, or behavioral techniques.

In spite of the wealth of anatomical knowledge concerning the third system, experiments have contributed little to our understanding of its function. The hypothesis that this portion of the brain forms the neural substrate of emotion has thus far failed to find much experimental support. This may be due, at least in part, to the lack of careful behavioral investigation of the effects of stimulation or resection of portions of this system; investigations which are long overdue. The finding that stimuli which result in an animal's "arousal" and in "activation" of the electrical activity of the isocortex produce electrical hypersynchrony in Ammon's formation provides another avenue of approach to the problem. Part of the difficulty has been the surgical inaccessibility of these structures, a difficulty which has recently been overcome. Thus, relevant data may be expected to become available in the immediate future.

Summary. We have examined the basis for the current interest in the "olfactory brain." Of two acceptable definitions of "rhinencephalon," the broader, including both allo- and juxtallocortex, has been chosen because it subsumes available data parsimoniously. On anatomical grounds, three allo- and juxtallocortical systems have been distinguished. The first (made up of olfactory tubercle, area of the diagonal band, prepyriform cortex, and the corticomedial nuclei of the amygdala) is considered a "primary" olfactory system on the basis of its direct connections with the olfactory bulb. A second system (made up of subcallosal and frontotemporal juxtallocortex and the septal and basolateral amygdaloid nuclei) is connected with the primary system but not with the olfactory bulb and is characterized by subcortical as well as cortical components. The lack of anatomical differentiation between cortex and subcortex in this system is found whether phylogenetic, histogenetic, axonographic, physiological, or behavioral data are considered. This system has been implicated in diverse functions: olfactory-gustatory, metabolic, and socio-emotional. Future investigation must determine whether some unitary function underlies the others, whether the multiplicity of functions reflects a multiplicity of subdivisions within the second system, or whether this system is, under different conditions, part of one or another larger system. Finally, a third allo- and juxtallocortical system (made up of Ammon's formation, entorhinal, and retrosplenial and cingulate cortex) can be distinguished from the others on a histogenetic, axonographic, and electrographic basis. The hypothesis that this system is the neural base of emotion has so far failed to receive conclusive experimental confirmation. This may be due in part to the lack of quantitative behavioral studies of the effects of stimulation or ablation of portions of this system and to their surgical inaccessibility. These shortcomings are being overcome and relevant data should be forthcoming.

We must end this review with the thought that the "olfactory brain," as defined, is not primarily olfactory though parts of it serve olfactory functions. Nor is the current conception of a "visceral brain" more tenable though viscero-autonomic functions are also served. It is clear that the formations in this portion of the brain, though they share several characteristics, are not, at this time, usefully thought of as *a* brain serving any *one* function. Since at least three distinct systems can be delineated, each might profitably be investigated separately before an attempt is made to define what functions they have in common. Current speculation has provided impetus to the systematic accumulation of data; however, if this accumulation is to continue, the formation of hypotheses must become more specific and remain sufficiently flexible to incorporate its product.

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THE PHYSIOLOGY OF OLFACTION IN INSECTS

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In 1799 Cuvier in his *Leçons d'Anatomie Comparée* said, "Of all substances which act on our senses, those which produce the sensation of odor are the least known, even though their impression on our economy may be the most profound and most alive." He then proceeded to explore the mystery of olfaction by analyzing the state of knowledge, anatomical and physiological, of his era. It is significant that Cuvier, the founder of comparative anatomy, extended his observations to vertebrates and invertebrates alike in the clear realization that there is no physiological or phylogenetic barrier which ordains that the study of either group be irrevocably delimited from that of the other.

During the intervening decades the example set by Cuvier was largely ignored. The comparative studies of Nägel (1897) stand out as a worthy exception. Only within very recent times is the cycle completing its full swing with the awakened awareness that physiological and biochemical processes within any group of animals are neither unique nor unrelated to processes serving the same end in other groups. Slowly, during the past twenty-five years, an increasingly great body of knowledge relative to the chemical senses of insects has been accumulated. It equals our knowledge of the vertebrate chemical senses in some respects and surpasses it in others. The time is at hand to extract from both fields the facts, techniques, and promising leads which will assist in the ultimate solution of the problem of the nature of chemoreception in either or both. A study of olfaction in insects has much, indeed, to contribute to the study of odors in general.

Although the earliest recorded observations relative to the olfactory senses of insects were those of Aristotle, the descriptive stage of olfactory studies had its beginning in the early eighteenth century when Réaumur (1734-1742) set about identifying the olfactory areas. Once begun, the study exploded into violent controversy which reached a climax as early as Cuvier's time when he himself concluded a discussion with these words, "The antennae, which other anatomists have believed to be the site of olfaction in insects, do not appear to us to possess any of the conditions required for that" (*cf.* Nägel, 1897). The debate continued unabated till 1935 (for detailed reviews, consult Kraepelin, 1833; Röhler, 1906; Forel, 1908; McIndoo, 1914a and b; von Frisch, 1921; Minnich, 1929; Marshall, 1935; Dethier and Chadwick, 1948a; Dethier, 1953). It is now generally conceded that the principal olfactory sites in insects are the antennae as Réaumur had correctly surmised. Other appendages on the head, especially the maxillary and labial palpi or their homologues, also bear olfactory organs in many species (*cf.* earlier reviews, von Frisch, 1921; Frings, 1941; Dethier, 1952a).

Proponents of the various sites of action usually supported their claims with detailed descriptions of the alleged end-organs. The controversy bore as its fruit the extensive histological examination of the areas in question, especially during an era when histology as a science was flourishing. As a result, when the antennae and palpi were finally proved to be the olfactory areas, we already possessed excellent descriptions of the multitudinous sensory structures situated thereon (*cf.*, for example, Hauser, 1880; Schenk, 1903; Vogel, 1923). The problem of deciding which of the various morphological types of sensilla were actually the olfactory end-organs then presented itself. The difficulty of this problem is attested by the prolonged delay in its solution. The fact that antennae such as those of the honeybee may possess eight morphologically distinct kinds of end-organs comprising in the aggregate some 500,000 sense cells (Vogel, 1923) graphically illustrates the difficulty.

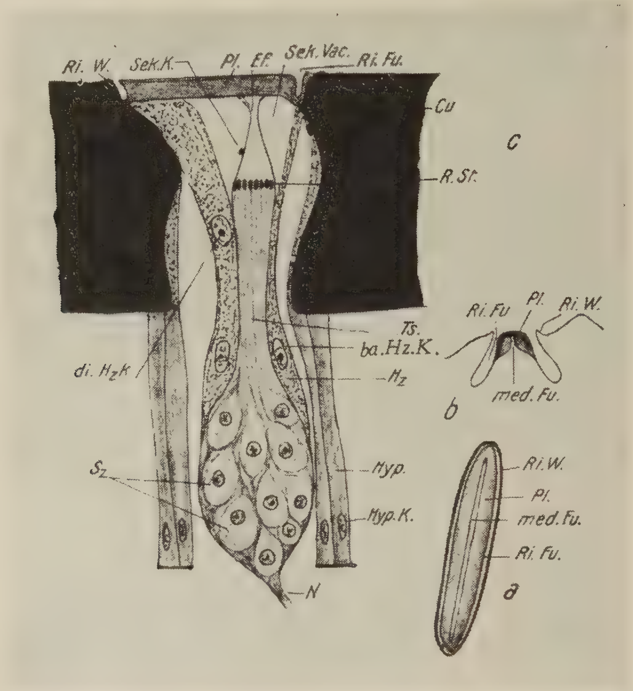

FIGURE 1. Sensillum placodeum on antenna of a wasp (Vogel, 1923). (a) Surface view. (b) Section through cuticular plate at right angle to long axis. (c) Section showing entire structure. N., nerve; Hyp., hypodermis; Hyp. K., nucleus of hypodermal cell; Sz., sense cells; Hz., enveloping cell; di. Hz. K. and ba. Hz. K., distal and basal nuclei, respectively, of enveloping cells; Ts., terminal strands of sense cells; Sek. K., secretory body; R. St., Riechstäbchen; Cu., cuticle; Ri. W. and Ri. Fu., socket and circumferential furrow respectively; med. Fu, median furrow; Pl., plate; Ef., attachment of fibers; Sek. Vac., secretory vacuole.

For nine species the experimental evidence is sufficiently well established to supply the answer. By amputating or sealing various numbers and kinds of sensilla, it was determined which of these were necessary in order that an insect might respond and orient normally to odors to which it had been conditioned or to odors of significance in its natural habitat. For the honeybee the necessary sensilla are the pore plates (sensilla placodea) (von Frisch, 1921); for the dung beetles *Geotrupes sylvaticus* and *G. vernalis* (Warnke, 1931, 1934) and *Necrophorus* and *Silpha* (Dethier, 1947a), for certain lepidopterous larvae (Dethier, 1941), for the human louse (Wigglesworth, 1941), for housefly larvae (Bolwig, 1946), and for *Drosophila* (Begg and Hogben, 1946) the necessary sensilla are all peg-like hair derivatives known as sensilla basiconica.

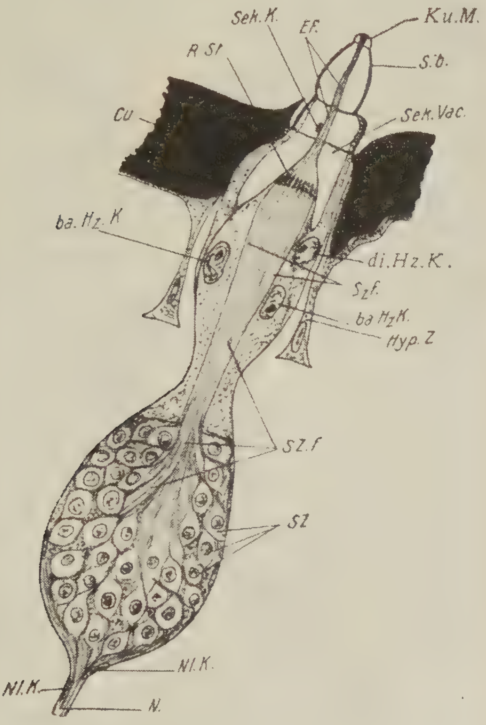

FIGURE 2. Sensillum basiconicum on antenna of wasp (Vogel, 1923). Letter designations same as n FIGURE 1.

The salient features of olfactory sensilla are illustrated by the types depicted in FIGURES 1 to 5. A sensillum placodeum (FIGURE 1) is a thin complicated membrane set into a socket in the cuticle and intimately associated with a group of cells which project upwards from the underlying tissues. The plate is frequently oval, may occasionally be slightly domed, may exhibit a median furrow, but always consists of a circumferential membrane only a raction of a micron in thickness. There is no opening to the underlying issues. The cellular elements of this sensillum consist of enveloping cells and a variable number of bipolar sense cells. The proximal processes of the

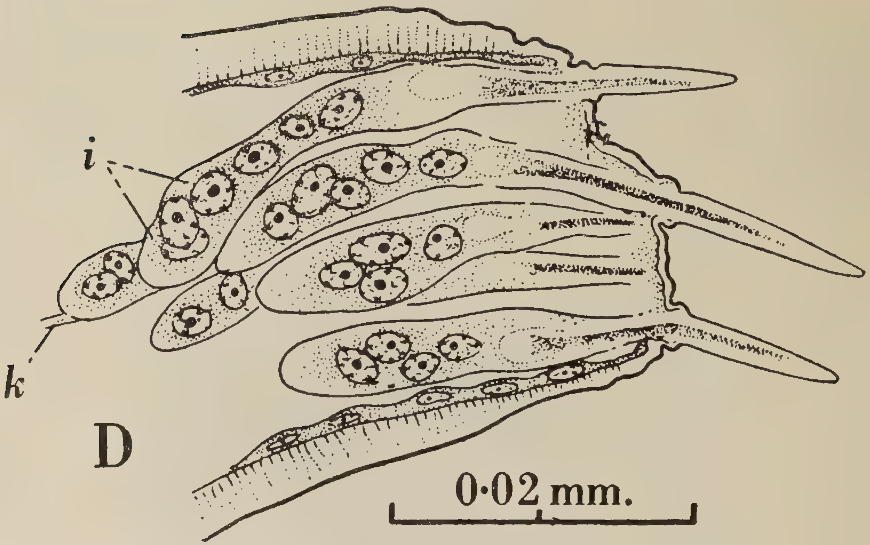

FIGURE 3. Sensilla basiconica on antenna of human louse (Wigglesworth, 1941). i, sense cells; k, proximal fiber from sense cells.

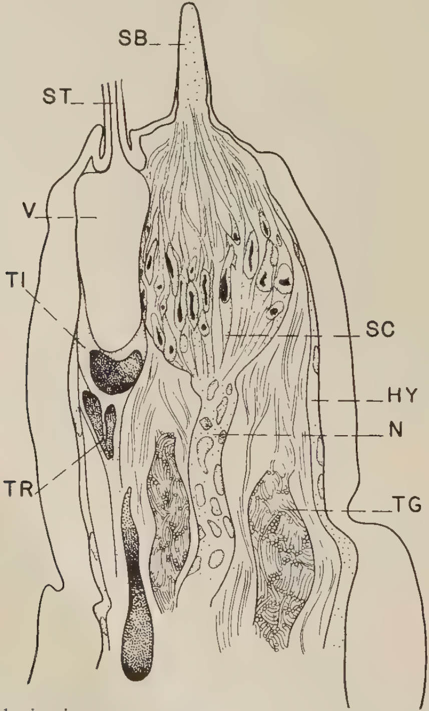

FIGURE 4. Sensillum basiconicum on antenna of lepidopterous larva (Dethier, 1941). SB, sensillum basiconicum; ST, tactile hair; V, vacuole; TI, trichogen; TR, tormogen; SC, sense cells; HY, hypodermis; N, nerve; TG, tracheoles.

latter appear to extend to a point under the surface of the plate and in this position lie in a vacuole containing fluid (Vogel, 1923). In addition, the distal processes are characterized by the presence of minute refringent bodies of unknown function, the Riechstäbchen. The proximal processes coalesce to form the afferent nerve, which proceeds without interruption to the supraesophageal ganglion. Whether or not the combined proximal processes retain their identities throughout their entire length or fuse completely to form a single axone is not known.

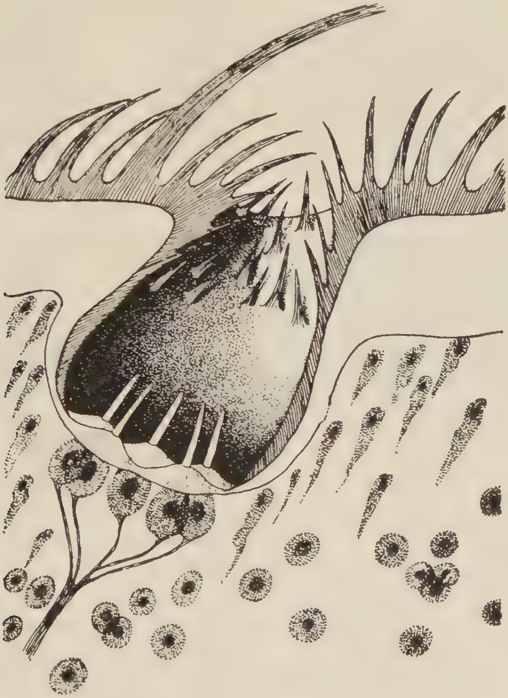

FIGURE 5. Olfactory pit on antenna of dipterous insect (Liebermann, 1926).

The sensilla basiconica (FIGURES 2 to 5) differ from the foregoing account chiefly in that the cuticular portion consists of a cone, peg, or blunt-tipped spine the walls of which are less than one micron in thickness. Again there is a variable number of bipolar sense cells, the distal processes of which project to the base of the cone or beyond and lie in a fluid filled vacuole. Thus, all olfactory receptors possess in common a cuticular covering which is completely or partially thin-walled. The majority are innervated by a group of bipolar sense cells. These cells are characterized by the presence of Reichstäbchen in the distal processes. It appears that the distal processes lie in a fluid-filled vacuole.

It is perfectly clear that the early physiologists were led astray by too rigid analogizing with vertebrates into the belief that a moist membrane closely overlying nervous elements is a *sine qua non* for olfaction (*cf.* Cuvier, 1799; and McIndoo, 1914a and b, 1934). It is equally clear that insects possess olfactory end-organs in which the nervous processes are separated from the stimulus by an unbroken, nonliving cuticle upon the surface of which there is no detectable effusion of mucus or comparable secretions. Numerous workers had postulated such a secretion principally because it was considered necessary for olfaction. Vogel (1923) suggested that the clear fluid within the sensilla basiconica on wasp antennae diffused to the outside. The reasoning was based on observations that staining reactions demonstrated ready permeability of the overlying cuticle to certain fluids. On the other hand, Snodgrass (1925) found no indication of secretions at the surface of sensilla placodea on the antennae of honeybees. Nor have later histologists demonstrated the presence of fluid on the surfaces of any other presumed olfactory sensilla. Apart from the possibility of an omnipresent monomolecular layer of water, the surface must be considered dry.

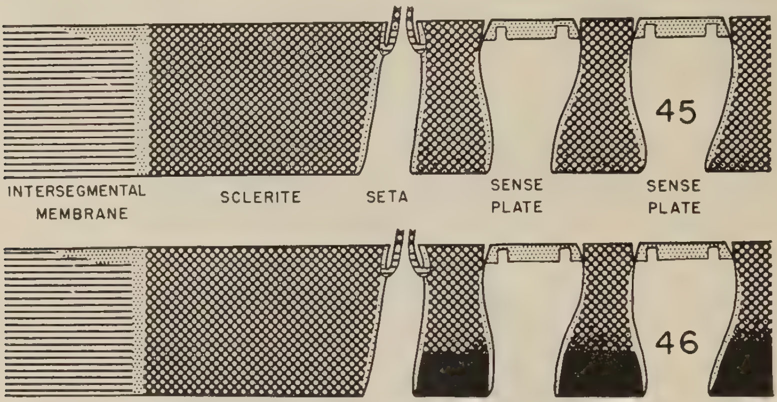

FIGURE 6. Diagram of cuticular portions of sense plate on antenna of the honeybee (Richards, 1952). Stippled areas, mesocuticle; cross-hatched areas, exocuticle; parallel lines, endocuticle; solid black, exocuticle modified by pigment.

Much of the reluctance to accept a sealed organ as olfactory arose directly from the penchant for ascribing to the covering cuticle the same properties of impermeability which are characteristic of the general body cuticle. Yet the body cuticle itself is remarkably susceptible to penetration by water, gases, electrolytes, dyes, and insecticides (Richards, 1951, 1953). Chadwick and Dethier (1949) pointed out the fallacy of thinking of the chemoreceptive surface in terms of the general body surface, and Richards (1952) finally succeeded in demonstrating the differences of end-organ cuticles. He analyzed by histochemical and electron microscopical methods the cuticle overlying the sense plate receptors on the antennae of honeybees. Previous speculations concerning the uniqueness of the end-organ surfaces were fully borne out by the results. The thinnest part of the covering membrane is less than one micron thick and consists of an inner chitin-protein layer and an outer epicuticle. These layers differ from the corresponding ones of other areas of the cuticle in that the chitin-protein layer is only partially sclerotized, and the epicuticle has a low lipid content (FIGURE 6). They also differ from corresponding areas in other types of sensilla. The low lipid content and incomplete sclerotization imply relatively ready penetration. Thus, as Richards pointed out, it follows that the cuticle over chemoreceptors cannot be assumed to have the same penetration properties as cuticle on other parts of the body. Furthermore, different sensilla with cuticles of similar thickness cannot be assumed to have similar penetration properties.

The number of olfactory sensilla in an insect varies from species to species. There may be as few as 9 to 10, as in the human louse, or there may be as many as 30,000 in the drone honeybee (Schenk, 1903; Vogel, 1923; McIndoo, 1914a and b). Attempts have been made to correlate the acuity of olfaction in the various species with the numbers of sensilla, but the correlation is highly conjectural in as much as the identity of the receptors is uncertain in many species, and quantitative tests of acuity have not been undertaken. It is certainly true that some correlation exists between the number of receptors and behavioral response to odors. Lice and lepidopterous larvae, which live on their hosts and have little apparent need for an extremely acute olfactory sense, possess few sensilla. Among the Diptera, Liebermann (1926) has shown that the so-called olfactory pits (*cf.* FIGURE 5) average 820 in dung-feeding species which depend largely upon odor for locating their food while in the flower-visiting species, which depend more on vision, the average number is 494. Moreover, the pits are more numerous in males than in females. This difference is presumed to be related to the fact that males employ the olfactory sense in the search for females. In any event, there is no doubt that all insects rely to a great extent upon the olfactory sense to assist in the location of food, egg-laying sites, and mates (see Dethier, 1947b, for a complete discussion). The ability of the males of some species of moths to locate the females by odors over distances as great as two miles is legendary. Thus, it is abundantly apparent that insects are capable with their "dry" end-organs of perceiving odors in extremely low molecular concentration and are indeed macrosmatic. A cuticular-covered end-organ must therefore be accounted an efficient one.

Although the behavior of insects in their natural habitat bespeaks an olfactory sense of extraordinary sensitivity, attempts to measure the limits of sensitivity in the laboratory have met with little success. Aside from the difficulty of quantitating the stimulus, a technicality which can be overcome by the development of more efficient apparatus, there is difficulty in deciding upon a criterion of response. Several thresholds have been used in this respect: threshold of response, acceptance, and rejection threshold. Ideally the threshold of response measured by electrophysiological methods is the most useful value. Attainment of such a value by these methods has thus far been denied us, but the Tufts College group has recently made a promising start in this direction. Potentials have been recorded from the antennal nerve of the cockroach (Roys, 1954) during perfusion by the vapors of toluene and related compounds. Although the concentrations of stimulating vapors employed are of the order of magnitude which elicit recognizable behavioral responses from the intact animal, the true olfactory nature of the reaction is in some doubt. The possibility remains that the response represents a common chemical sensitivity.

The first recognizable behavioral manifestation in response to odors takes the form of antennal movements, such as waving and vibrating, or movements of the mouth parts frequently accompanied by salivation, or various cleaning reactions in which the legs or antennae may be drawn through the mouth parts. As the concentration of an odor is increased, it elicits from the insect locomotor activity whereby the insect either flies, walks, or swims toward or away from the source of stimulus. The nature of the locomotor reaction (that is, whether it represents attraction or rejection) depends upon the concentration of the stimulus as well as the nature of the stimulus and the genetic constitution of the insect. What is attractive to one species may be without effect or repellent to another species. A compound which is attractive at one concentration may be repellent at another. If a compound is initially repellent, it remains so as the concentration is increased. If a compound is initially attractive, it increases in attractiveness as the concentration is increased until a maximum attractiveness is attained. A further increase in concentration usually leads to rejection. For every chemically pure attractant thus far tested, there can be found a concentration at which it becomes repellent (Dethier, 1947b). Typical is the response of *Musca domestica* to the vapor of iso-valeraldehyde. At concentrations below 2.0×10^{-6} M, no behavioral response is elicited; at 1.2×10^{-5} M, there is maximum attraction; over the range 2.0×10^{-5} M to 2.8×10^{-5} M, this aldehyde is partly attractive and partly repellent. Repellency is increasingly effective as the concentration is further increased and is maximum at

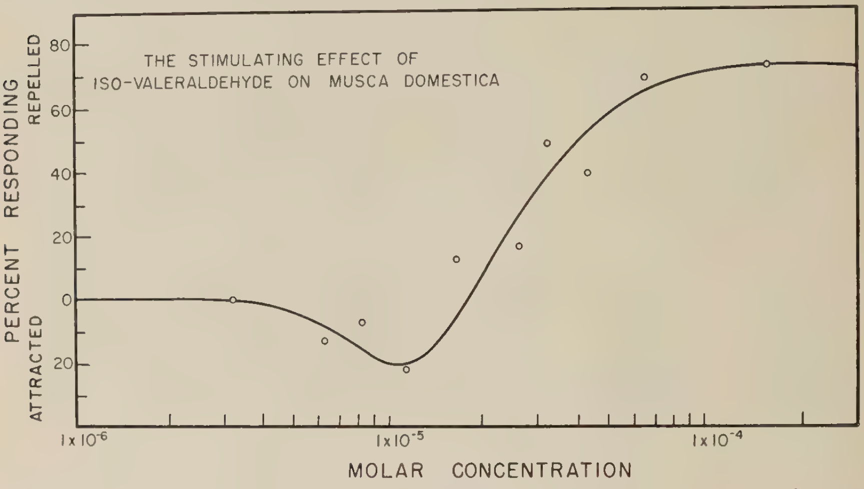

FIGURE 7. The stimulating effect of iso-valeraldehyde on the common house fly. At low concentrations the odor is attractive while at higher concentrations it repels.

6.0×10^{-5} M (FIGURE 7) (Dethier, Hackley, and Wagner-Jauregg, 1952).

Much has been made of the fact that, for human beings, certain odorants undergo changes in modality as the concentration changes. A commonly quoted example is skatole which may smell pleasant at low concentrations and is considered acceptable, but possesses a fecal odor at higher concentrations and is then considered repellent. Although nothing is known with certainty (*cf.* von Frisch, 1921) concerning the odor modalities for insects, beyond the fact that there is a modality "acceptable" and a modality "unacceptable," the change in the nature of response to different concentrations of the same compound, as exemplified by the reaction of *Musca domestica* to iso-valeraldehyde, is strikingly similar to the changes in modality reported for man. While the possibility of relating these differences in man to numbers or identity of receptors appears remote, a solution to the problem seems practicable in insects. With *Phormia* it has already been shown (Dethier, 1952a) that the gross olfactory area necessary to mediate both reactions is identical; *i.e.*, the fly requires antennal receptors in order to perceive both acceptable and unacceptable concentrations. The unacceptable concentrations are not, therefore, stimulating nonspecialized receptors situated somewhere else on the body. The next step, showing precisely which or how many receptors must be stimulated to mediate acceptance and which to mediate rejection, awaits only experimentation. Because of the accessibility of receptors, very precise local extirpation is possible. Furthermore, precise threshold measurements can be made.

The earliest attempt at precise quantitative measurements of threshold was that in which Barrows (1907) determined by means of a simple olfactometer that a 20 per cent aqueous solution of ethanol attracted more individuals of *Drosophila melanogaster* than did any other concentration. The most attractive solution of acetic acid was 5 per cent. Wirth (1928) succeeded in obtaining precise measurements of the behavioral threshold of response of *Habrobracon juglandis* to gases of known concentration. The criterion of response consisted of cleaning movements and associated activity of the antennae. In the ensuing years threshold data were accumulated for a variety of insects by Folsom (1931), Warnke (1931), Reed (1938), Wieting and Hoskins (1939), Dethier (1941, 1943), Crombie (1944), Dethier and Yost (1952), and Hodgson (1953). A comparison of these data is of limited value because different criteria of response were selected by the different investigators. For the same reason a comparison of these threshold values with values obtained with human beings does not give an accurate picture of the relative sensitivity of insects and man.

Probably the greatest value which can be attached to the determination of threshold data relates to their use for investigating the mechanism of interaction of odors and olfactory receptors. Determination of thresholds by behavioral methods is attended by major pitfalls. When thresholds are employed for interpreting mechanisms of action, it is well to remember that the peripheral activity provoked by the stimulus is translated through an entire organism before an answering response is forthcoming; consequently, the limiting mechanism being measured may represent any one or more factors operating anywhere between the receptor and the effector. For these reasons the value of threshold measurements has been questioned frequently. Nonetheless, judiciously employed, the technique of threshold measurement can throw light on the mechanism of olfaction.

Use of the lowest behavioral threshold (threshold of response, difference threshold) is probably less rewarding than use of an acceptance or rejection threshold. Several recommendations for the latter come to mind. For example, such thresholds represent responses over a middle range of available concentrations rather than at a lower limit; accordingly, the reliability of measurement from a statistical point of view is greater than at either end of the concentration range. Furthermore, from a purely technical point of view, one need not be unduly concerned with traces of contaminants. Contaminants can seriously affect the recognition threshold where they must be considered to be present in significant concentrations relative to the test stimulus. Where the test stimulus is present in high concentration, as in acceptance and rejection studies, the contaminant is proportionally insignificant.

The study of vision has profited greatly through the use of intensity comparisons. Extension of this technique to olfaction also bids fair to be valuable. It must be difficult, however, to compare solely on an intensity basis such modally different odorants as, for example, allyl alcohol and linaloöl. With insects, a comparison of rejection thresholds represents intensity matching. The rejection threshold is by definition the concentration which causes some all-or-none response such as retraction of the proboscis or flight away from the source of stimulus. Consequently, there is reason to hope that studies of rejection thresholds may yield to olfaction information of the same type and value as that earned by intensity matching studies in the field of vision.

A serious attempt in this direction was made by Dethier and Yost (1952). Their study of the responses of the blowfly *Phormia regina* to homologous alcohols illustrates the advantages of employing insects in work of this sort. As these authors pointed out, the foremost obstacle to research on olfaction has been the inability to quantitate and define the stimulus. Second in importance have been the inaccessibility of the vertebrate olfactory receptor area and the difficulty of selecting a useful criterion of response. Once satisfactory instruments have been developed to overcome the first obstacle, the problem remains of presenting the measured stimulus to the sensory area and eliciting an unequivocal response. With man the remoteness of the sensory area, and the association of stimulus transport with the process of inhalation, introduce complications. In the insect, as exemplified by the blowfly, the receptors are situated on easily accessible surfaces of the antennae, labellum, and palpi. Inasmuch as the receptors for taste (contact chemoreception) are situated on different areas, the tarsi and labellum, either sense can be studied separately with the sure knowledge that there is no interference. Thus, by extirpating the olfactory receptors of flies, workers have studied the effects of many organic and inorganic compounds on contact chemoreceptors (Chadwick and Dethier, 1947, 1949; Dethier, 1951; Dethier and Chadwick, 1947, 1950). The results of these studies will be compared with the data on olfaction in the following pages.

A brief description of the method of measuring olfactory thresholds is essential to an understanding of the discussion which follows. For details, the paper of Dethier and Yost (1952) should be consulted. Caged flies were placed in an olfactometer which delivered two distinct streams of gas to and through the cage. When both streams consisted of pure air, the flies distributed themselves evenly on the wall of the cage adjacent to the incoming air. A photograph taken at this time shows approximately equal numbers of flies assembled before each incurrent port. When the air at one incurrent port is replaced by a stimulating odor, the distribution of flies before the two ports becomes unbalanced. If the odor is an attractant, more flies congregate before the test port. If the odor is a repellent, flies leave the test port and congregate before the control port. The concentration of test odor which caused the number of flies at the test port to be increased by 50 per cent was termed the median acceptance threshold. Conversely, the least concentration which caused the number of flies at the test port to be decreased by 50 per cent was termed the median rejection threshold.

Measurements of the olfactory rejection thresholds by means of the apparatus and techniques just described have revealed an orderly sequence of values within a homologous series. As the chain lengths of the normal aliphatic alcohols are increased the thresholds, expressed as molarities, decrease logarithmically until the so-called cut-off point is reached at or near undecanol. As is well known, a logarithmic relationship between physiological activity and chain length within homologous series is characteristic of narcotics and toxic agents. In these cases, as Ferguson (1939) has pointed out, the activity under study represents the establishment of an equilibrium between the circumambient phase and the internal biophase. As far as olfaction is concerned, there is as yet no conclusive evidence that the process involves equilibria. Short of actual definitive experiments, however, there are several characteristics of the olfactory process which partake of the nature of equilibria. For example, the maximum physiological effect is obtained very rapidly, it remains at an even level for considerable periods of time under continuous stimulation, it is rapidly reversible when the stimulus is removed, and it exhibits characteristic relationships with special physical properties of homologous series.

Most physical constants of a homologous series undergo approximately equal changes in passing from one member to the next. A few, however, show the same logarithmic change which characterizes thresholds of narcosis, toxicity, and olfaction. Water solubility, surface activity, vapor pressure, and partition coefficients are properties which change logarithmically with chain length. Meyer and Hemmi (1935) have argued that a logarithmic relationship is indicative of the existence of an equilibrium, since, for each of the properties mentioned above, the constants represent an expres-

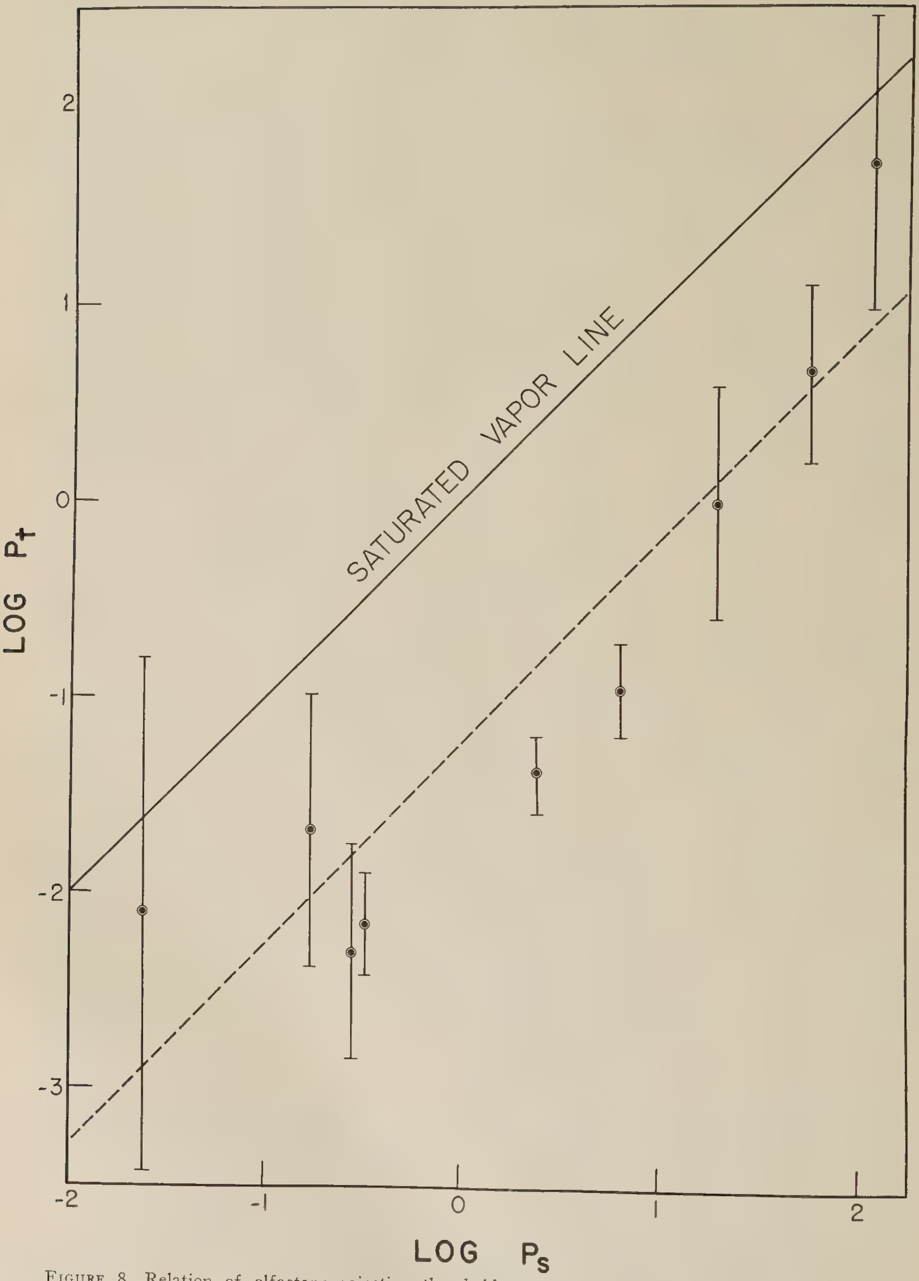

FIGURE 8. Relation of olfactory rejection thresholds expressed as pressures (p_t) to saturated vapor pressures (p_s). The vertical lines indicate two standard errors. (Dethier and Yost, 1952).

sion of a distribution between two heterogeneous phases (*e.g.*, vapor pressure, which represents an equilibrium between a pure solute and its saturated vapor). If an equilibrium does indeed exist, a primary action of a physical character may, according to Ferguson (1939), be assumed. In toxicity studies, the existence of a direct correlation between solubility or vapor pressure has been used as a criterion to determine whether or not the toxic action under examination is to be referred to a physical or chemical mechanism.

The similarity between the serial nature of olfactory thresholds and that of narcotic and toxicity data prompts one to apply to olfactory data some of the tests which have proved valuable in the other fields (*cf.* also Ferguson, 1951; Gavaudan, 1951; Poussel, 1951). When the rejection thresholds of *Phormia* are converted to pressures measured in mm., and plotted on logarithmic coordinates against their respective saturated vapor pressures (FIGURE 8), it becomes apparent that the thresholds vary directly with vapor pressure. As has been pointed out above, direct correlations with vapor pressures characterize many phenomena which are known to represent equilibria. Accordingly, a further analysis of the olfactory data would seem to be indicated. Such an analysis depends upon the use of thermodynamic activities as units of threshold measurement.

It is probably opportune to point out at this juncture that a poor choice of units of measurements can effectively obscure the nature of basic mechanisms which are limiting the processes being measured. It seems illogical to measure chemical stimuli in terms of percentages or parts per million, however convenient, rather than in terms of molarities or equivalent units when it is reasonably certain that the stimulus is molecular. Even the use of molar concentrations may be questioned. In so far as narcosis and toxicity are concerned, data presented by Ferguson (1939, 1951) and Ferguson and Pirie (1948) have shown that within a homologous series toxicity may increase with chain length if molar values are employed, but may decrease with chain length if activities are employed. Clearly, careful consideration must be given to the selection of units to express concentration if valid conclusions are to be drawn from a body of data.

The linear relation in a homologous series between the logarithms of various distributions and the number of carbon atoms indicates simply a constant increment for each successive homologue in the partial molal free energy difference between the standard states in the two phases. The thermodynamic activity referred to above is partial molal free energy referred to a standard state. It represents the amount of work required per mol to transfer a compound from one phase to another. For a perfect gas or a perfect solution, it is described by the equation

$$\bar{F} = F_0 + RT \ln c$$

where F_0 = partial molal free energy in a standard state and c = molal concentration. For a non-ideal gas or solution, the concentration is expressed by activity (a):

$$\bar{F} = F_0 + RT \ln a$$

The thermodynamic activity is numerically equivalent to the relative saturation of the vapor pressure at the temperature of the experiment. If, for example, p_t is the pressure

$$\left[p_t \text{ (mm.)} = \text{conc in mol/l} \times 22.41 \times \frac{t + 273}{273} \times 760 \right]$$

of the compound producing an effect (*e.g.*, olfactory threshold, intensity of odor, *etc.*) and p_s is the saturated vapor pressure at the temperature of the experiment, then p_t/p_s equals the activity. Accordingly, at any given temperature, the activities of all saturated vapors are arbitrarily unit (Ferguson, 1939; Steiner, 1948).

The rationale behind the use of this unit in physiological experiments has been discussed in detail by Ferguson (1939, 1951), Ferguson and Pirie (1948), and Brink and Posternak (1948). If one expects to derive fundamental information from the determination of thresholds, intensity comparisons, *etc.*, a comparison of concentrations in applied ambient fluids or gases is not entirely valid because of the fact that the applied stimulus is acting at one or more interfaces the nature of which determine the actual effective concentration. There is probably no better way of emphasizing this point than by calling attention to the differences in taste thresholds which can be produced merely by changing the solvent containing the taste substance. Illustrative data for man and insects taken from the papers of Dethier (1951 and 1952b) are presented in TABLE 1. Clearly, relative effectiveness measured by external thresholds depends on the phase chosen for measurement. If a compound is distributed in equilibrium between two or more phases, its activity, suitably defined, has the same value in all phases (Ferguson, 1939). Consequently, although one may be ignorant of the biophase, he may state with certainty, from the externally measured concentration, what the activity will be at the site of action.

TABLE 1

EFFECT OF THE SOLVENT ON THE TASTE THRESHOLDS (MOLAR) FOR NORMAL ALIPHATIC ALCOHOLS.
DATA FROM DETHIER (1951, 1952b)

Compound	*Man*		*Blowfly tarsi*		
	Difference	*Threshold*	*Rejection*		*Threshold*
	In water	*In mineral oil*	*In water*	*In glycol*	*In mineral oil*
ethanol	0.32	0.093	2.4	2.8	—
propanol	0.11	0.043	1.2	0.75	—
butanol	0.028	0.019	0.48	0.79	0.72
pentanol	0.016	0.013	0.076	0.25	0.55
hexanol	0.002	0.0098	0.0062	0.069	0.46
heptanol	0.0013	0.0092	0.0012	0.052	0.11
octanol	0.0006	0.015	0.00012	0.044	—

It has already been pointed out that there is no direct evidence that the olfactory process involves equilibrium states. Yet, in view of what has been said regarding the relationships between molar thresholds and chain length in homologous series, an analysis in terms of activities is warranted. When this is done and the logarithms of activities at threshold plotted against the logarithms of the respective activity coefficients (FIGURE 9), it may be seen

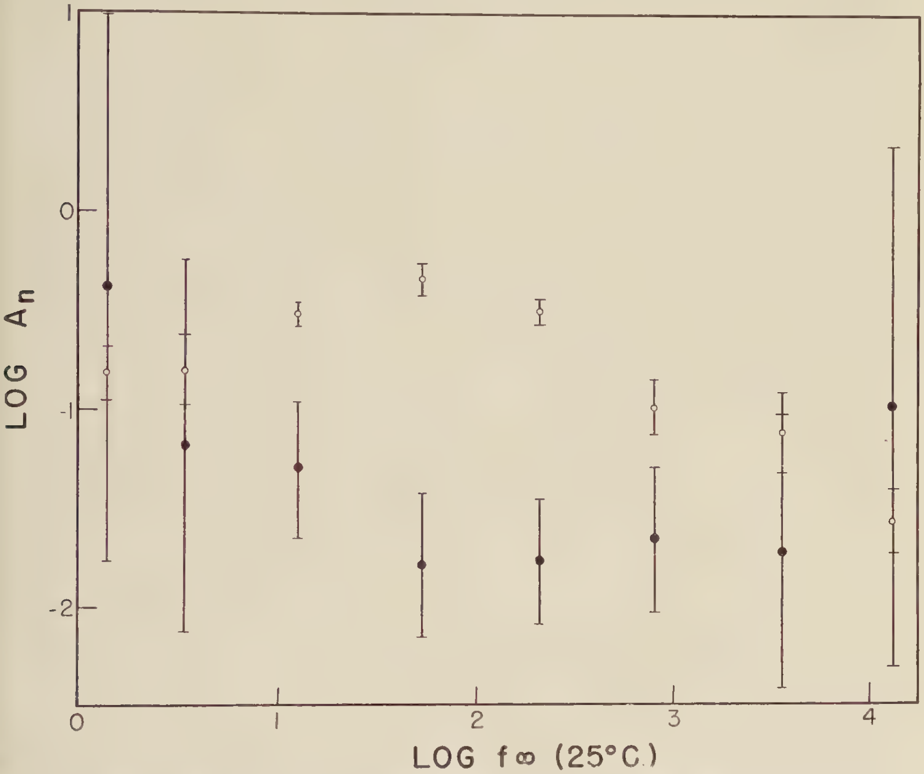

FIGURE 9. Comparison in terms of thermodynamic activity of the stimulating effectiveness of the first eight normal alcohols acting in aqueous solution (open circles) on tarsal chemoreceptors and as gases (solid circles) on olfactory receptors. In each case the value represents a threshold of rejection. The vertical lines represent 2.575 standard errors for aqueous thresholds and 2 for vapors. (Dethier and Yost, 1952).

that the thresholds of all homologues are nearly equal. They extend at most over one and one-half log units as compared to a range of four log units when expressed in terms of molarities. The rejection thresholds of the same compounds, acting as aqueous solutions on the tarsal contact chemoreceptors of the same insects have been included for comparison. While aqueous solutions of the alcohols do not stimulate contact receptors at equal activities, the action of the alcohols as vapors on the olfactory receptors more nearly conforms to the rule of equal physiological activity at equal thermodynamic activities. This relationship has been interpreted by Dethier and

Yost (1952) as suggesting that the limiting process of olfaction, at least in so far as the normal aliphatic alcohols are concerned, may involve an equilibrium process. Similar relationships are suggested by data which have been collected by measuring the acceptance thresholds of aliphatic aldehydes. These data, however, have not yet been completely analyzed. On the other hand, an analysis of partial data obtained from field tests of the attractiveness of aliphatic alcohols to flies (Cook, 1926) reveals a decrease in thermodynamic activities at threshold as the homologous series is ascended.

Some of the relationships, so clearly demonstrated in the blowfly, between threshold concentrations and certain physical properties of homologous compounds have been hinted at by the few available data collected in studies of human olfactory thresholds and intensity comparisons. Thus, the minimum perceptible concentrations of homologous alcohols (see International Critical Tables) decrease logarithmically as chain length increases. Scattered data on alkyl mercaptans (Allison and Katz, 1919) suggest a similar tendency but are incomplete. The knowledge that intensity of odor increases up to a point in homologous series and then decreases (Moncrieff, 1944) fits into the same pattern. Intensity comparisons reported in this monograph (Beck, Kruger, and Calabresi, 1954) also point to the same conclusion. Great variability within human subjects, however, and the difficulty of obtaining significantly large numbers of subjects so that the variability from one individual to the next can be measured and limits of confidence set, have conspired to render difficult the accumulation of accurate and complete values. Thus, the few values which are available do not lend themselves to as rigorous an analysis as do those obtained with insects.

Nevertheless, when the available threshold data relating to members of a homologous series are converted to units of activity, the resulting values fall within a much narrower range than they do if expressed as molarities. The unexpected feature which emerges from this treatment is the appearance of a progressive decrease in activities as the chain length of the compounds is increased. A similar trend was noted in the data of Cook mentioned above. The data of Ferguson (1939 and 1951) on toxicities usually showed an increase in threshold activities as series were ascended, while the data collected by Brink and Posternak (1948) showed an increase in some instances and an equality in many. Brink and Posternak have pointed out, however, that data occasionally do exhibit a progressive decrease. It is just these differences in trends from one biological system to the next which illustrate the wisdom of subjecting data to thermodynamic analyses. For it is through the exceptions even more than through the similarities that the nature of the divers processes may be exposed.

A question always remains as to how far an analysis made with one species can be extended to other species, especially when the two are as widely separated as man and insects. Yet the similarities in other physiological systems of the two organisms (consult, for example, Roeder, 1953) have been proven to be strikingly close and, whether or not the insect olfactory mechanism is basically dissimilar to that of man, an elucidation of that system could smooth the way to an understanding of the human olfactory process. While work with fellow human beings possesses the obvious advantage of a common medium of communication between experimenter and subject, it may not match the anatomical advantages and numerical superiority offered to the insect physiologist. But he, faced with a language barrier, is forced to resort to subterfuge in pitting his brain against that of his hexapod subjects.

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AN INFORMATION THEORY OF OLFACTION

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> "You cannot suppose that atoms of the same shape are entering our nostrils when stinking corpses are roasting as when the stage is freshly sprinkled with saffron of Cilicia and a nearby altar exhales the perfumes of the Orient. . . . You may readily infer that such substances as agreeably titillate the senses are composed of smooth round atoms. Those that seem bitter and harsh are more tightly compacted of hooked particles and accordingly tear their way into our senses and rend our bodies by their inroads."

In these words, Titus Lucretius Carus[1] developed the first atomistic theory of olfaction at about 47 B. C. This year of 1953 marks the two-thousandth anniversary of this theory. In view of the present status of the theory of odor, the concept which Lucretius advances is remarkable; it involves the transfer of atoms, their shape, and their mode of interaction.

According to R. W. Moncrieff,[2] there have been proposed perhaps twenty-five theories of odor during the period of the last one hundred years. These theories, like that of Lucretius, center around the receptor and its interaction with the odorant molecule. They can be classified into three major groups, each involving one mode of interaction: (a) the chemical stimulation of the receptor by the bombardment of odorant molecules, (b) the vibratory stimulation of the receptor by the presence of the odorant molecules, and (c) the wave or photon stimulation of the receptor by radiation from or to the odorant molecule. In addition, there have been six or eight major classification systems for olfactory experience which attempt to "explain" every odor by reference to the presence or to the intensity of several general classes of subjective experience, *e.g.*, spicy, fragrant, burnt, almond, mint, *etc.*, much in the manner of the four attributes of taste.

Not one of the theories of odor or systems of classification has met with unusual success in its avowed purpose, and not one is currently being defended as a way of explaining all of the observed properties of olfaction. We suggest, therefore, that a new approach be taken to the entire olfactory process. We propose that olfaction in all its aspects be considered from the point of view of the modern approach to the communication of information. The modern advances in communication, *e.g.*, the telephone and television, and the handling of information within computing machines, have made possible the information theory of olfaction.

The nature of olfaction has, therefore, been studied from the informational aspects of three areas of experience; the new theory has been synthesized from the knowledge of: (1) the subjective olfactory experience, (2) the neurophysiology of the olfactory system, and (3) the requirements for the storage and transmission of information.

In simplest terms, the best way to understand the significance of the odorant molecule's action on the odor receptors is to examine the informational capacity of the nerves which connect the olfactory patch and the cerebrum. For if, regardless of mechanism, molecular bombardment results in the accumulation of information in the receptors, and if the cerebrum receives this information, its meaning will be deduced in the "learning process."

The following are the important features on which this odor theory is based.

(1) The important observations from subjective experience are: Nearly everyone can sharply differentiate between a very large number of odors near threshold concentration. The memory of a specific odor can be permanent; that is, recognition can take place after many years. By contrast, the intensity of a given odorant is not only poorly perceived but almost impossible to remember. The perception of intensity appears to be a logarithmic function of the external chemical concentration.

(2) In simplest terms, the important observations from neurophysiology are: A neuron is either "on" or "off" in a given interval; an overstimulated neuron fails to respond but in time will recover. In each nostril of a rabbit there are about 50,000,000 olfactory receptors, each with one primary neuron which extends to the olfactory bulb. Between the olfactory bulb and the brain there are 45,000 secondary neurons which are made up of 24 fibers from each of the 1900 exchanges or glomeruli which link up the receptor neurons with the nerve fibers of the central nervous system.[3]

(3) The important assumptions from information theory are: In order for an odor to be remembered, it must be a simple pattern in the "on–off" response of the secondary neurons. In order to transmit many odor patterns, neurons must work in parallel, in groups. To account for as many odors as there probably are, perhaps twenty neurons must operate together; since 24 is the number of neurons which extend to the brain from each glomerulus, we assume there are 24 different kinds of nerve pathways. Thus, there are 1900 sets of 24 neurons to the cerebrum, and the intensity of olfaction is transmitted as the degree of activation of these 1900 identical sets of neurons. A distinct odor is, therefore, a given pattern of "on-ness" on what might be considered as a panel board of 24 "lights."

An intensity network has been formulated from these simple numbers and two laws: (1) the law of normal fluctuations in a statistical system and (2) the logarithmic law of perception, the Weber-Fechner law. From this, and from the theory alone, we find that there are 29 "just noticeable perceptual differences" (JND) between 30 perceptual levels of experience, that the effective chemical concentration range (that is, the ratio of the lowest concentration which gives the maximum perception to threshold concentration is about 190,000), and that the increase in concentration required to make a just noticeable difference is about 52 per cent. These theoretical predictions have been checked with direct observations on several odorants and are in good agreement.

The neural model that is consistent with these laws can be used to explain the secondary olfactory features of masking, cancelling, enhancing, fatigue, adaptation, quality loss on inhalation (or dilution), and anosmia. In addition, this theory suggests a number of critical experiments for testing its validity; already some work along these lines has been started.

The Information Approach to Olfaction

The general informational theory proposed here is applicable to all sensory systems. It states that a valid approach to perception can be found by evaluating the informational capacity (that is, the capacity for different patterns of the transmitting neurons alone), and by comparing this capacity for different patterns with the subjectively perceived and counted information of the sense in question (in our case, the number of odors and intensity differences). This approach produces an immediate insight into how to proceed to construct a specific model of this sense, and has great flexibility since it can be modified in many ways to accommodate quantitative data.

From this point of view, we developed a specific theory of the olfactory system involving a detailed model, some features and predictions of which have been suggested above. The utility of this model is attested, not by whether it is ultimately proved correct in numerical detail, but whether its implications encourage a more rational approach to olfaction or aid in unfolding the true nature of the olfactory system. This model provides a new basis for research on the many aspects of olfaction.

We shall now examine in more detail the important features of the three areas of knowledge required for this theory.

Subjective Olfactory Experience

In reviewing the evidence gathered in an experimental flavor laboratory, one is struck by the fact that, in general, native ability to distinguish between odors is remarkably uniform. The learned aspects of olfaction vary greatly between people; the odor expert has developed greatly his powers of recognition and identification, but his feeling of confidence is no greater than that of the amateur when asked to differentiate between two odorants; *e.g.*, oil of wintergreen (methyl salicylate) and banana oil (amyl acetate).

The number of different odors that can be detected is very large. Estimates have been made that the average person is able to differentiate between several thousands of odors. There are experts who affirm that it is possible to recognize at least 10,000 odors.[4] The number of organic compounds reaches into the millions, and possibly each has a different odor. As an estimate, we have taken the number of recognizable odors to be larger than 10,000.

It is a truly remarkable property of smelling that discrimination takes place at the threshold for sensory perception. This means that the olfactory system not only detects the presence of an odor but distinguishes between the odor detected and many other odors at their lowest perceived level. The memory for specific odors is also quite remarkable. Once an odor has been experienced, it is possible to identify this material with great personal confidence after many years. We can all recall experiences where the perception of an odor recreates an image of a situation from many years earlier. Such an experience is not approximate or tentative but carries with it the full conviction of the earlier experience.

Such clarity of perception is not true of the intensity of an odorant. An individual carries no sure conviction of how strong a sample was yesterday or whether the sample is stronger or weaker than a sample examined earlier, except on the grossest basis. There is no convenient name or identification for intensity and often many trials are required to establish the difference between even relatively large changes in concentration.

The Weber-Fechner law for the intensities of odors is well known. It states that the perceived intensity is proportional to the logarithm of the external concentration or that the ratio in concentrations, which produces a detectable difference, is a constant.

The Knowledge of Neurophysiology

There are two kinds of information about the neurophysiological processes that are important. First, in what manner do neurons carry information and, second, how many elements does the olfactory apparatus contain and how are they arranged?

Transmission by Neurons. The electrically observed propagation properties of neurons have been carefully worked out by Adrian, Erlanger, Gasser, and many other workers. A stimulated sheathed neuron transmits, in one direction only,[5] a negative pulse of approximately 1 millisecond[6] in duration and then recovers during approximately the next 15 to 100 milliseconds.[7] During this interval, it is not again discharged by a minimum stimulus. The pulse time is thus about 1/50 of the total recovery time. The pulse has no meaningful degrees of magnitude; one is not more than another in the manner of the deflection of a meter. The pulse is either transmitted or not transmitted, either "on" or "off."

Too rapid stimulation of an olfactory neuron may not produce a response, but may actually block the neuron and prevent transmission[8] until a time interval without stimulation has elapsed. Synapses between neurons in a single track normally pass the pulse from one neuron to the next without essential modifications. There are synapses, however, which have been shown experimentally to require two pulses simultaneously in two input neurons[5,9,10] to produce a single pulse in the output neuron. For our purposes, these are called two-junction synapses.

Not all neurons are covered with a myelin sheath. The primary neurons of the olfactory system, leading from the receptors to the olfactory bulb, are unsheathed. Since they have not been individually characterized, their properties are not well known. The work of Adrian,[11] however, suggests that the messages transmitted by these neurons may be in the form of waves rather than pulses. These waves are converted to pulses in the olfactory bulb, probably at the mitral cells, whose axons form the olfactory tract leading to the cerebrum. From the informational point of view, the important fact is that the final transmission is by pulses. It makes little difference what the nature of the transmission in the primary neurons may be since, for example, waves could be replaced by a set of pulses which are informationally equivalent.

The Olfactory Anatomy. The olfactory systems in mammals bear a close relationship to each other as far as exact data have been obtained. Le Gros Clark and his co-workers have carefully described the olfactory system of the rabbit, incorporating the results of previous workers. There are in each nostril 50,000,000 end organs,[12, 13] each of which has 10 to 12 hairs, 0.1 micron in diameter, projecting into the nasal passage from a "terminal swelling" in the neuron. These hairs are unprotected parts of the same neural cells which extend through the cribriform plate to the olfactory bulb. The nasal patch is about 4 to 5 cm^2 in area and the end organ density may be as great as 150,000 per $mm.^2$ The number of end organs for man is not markedly different except that there are only five or six terminal hairs. Adrian[14] recently reported that the thresholds of the rabbit for a number of odorants are equivalent to those found for man.

The olfactory lobe or bulb is a region of great complication and many connections; it is a type of "exchange." Within a volume of approximately one cubic centimeter, it has 50 million input cells from the nasal patch and 45,000 output cells to the cerebrum. The outer layers of the bulb are a profusion of neurons going in all directions. Further within, there are 1900 sub-exchanges, or glomeruli, each of which has 24 output neurons which lead through 24 granular cells to 24 mitral cells which lead to the cerebrum. In addition, there are 24 side loops projecting from one location on the mitral cell to a previous point on possibly the same, or an equivalent, track. Each glomerulus has a number of tufted cells which connect to the bulb of the opposite nostril.

The complicated cerebral connections of the olfactory system are not dealt with here because their functions are not specifically understood and are believed to be fundamentally cerebral in nature.

The Requirements for the Communication of Information[15]

For two people to pass information back and forth to each other, they must agree on a code. The code may be letters and words or other symbols. To convey a meaning, a code representing that meaning is transmitted. The contribution of modern information theory is that any channel of communication, a telegraph wire, or a television channel can be considered as presenting a very large number of possible patterns where, in a given interval, one single pattern of all the possible patterns is transmitted. If a given pattern, for example, dot-dash, is encoded to mean the letter "A," we may transmit the meaning "A" by transmitting the code. The only problem is to make sure that the code is faithfully transmitted throughout the system; that is, that the pattern does not change during transmission.

One way to determine the informational capacity of a system is to determine the number of possible patterns which can be transmitted. Another way is to determine the number of different meanings which the system is observed to transmit or represent. Both approaches have been used to formulate this theory.

The properties of the receptors are important from the informational point of view because the receptors are the units that encode the interactions with the chemical molecules into patterns on the olfactory neurons. We assume from the psychology of perception that, if a consistent code which indicates the presence of specific chemical molecules is formed by the receptors on the neurons, the brain, by experience, will learn to recognize the presence of these chemical molecules. If part of the information to the brain fluctuates with changes in external concentration of the odorant, the brain will learn to judge these changes in concentration provided the change is detectable; that is, it is larger than the random fluctuations within the system.

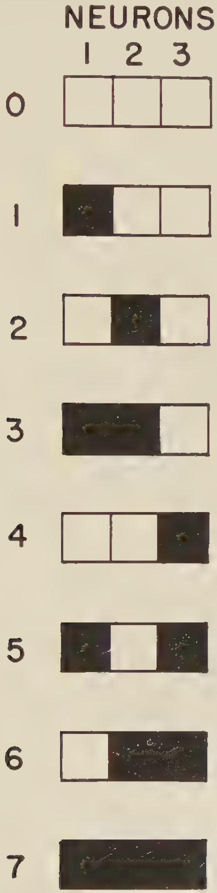

FIGURE 1. Digital patterns or configurations obtained from three neurons operating in parallel.

The Formulation of the Model

These many divergent properties may now be combined to form a specific model for the olfactory system. Since a given secondary neuron can give only two responses, "off" or "on," it is necessary, in order to obtain greater capacity for information, to combine a number of neurons together into a group. FIGURE 1 illustrates how this can be done. Thus, eight different "off-on" patterns can be presented by three nerves; or $2^3=8$.

The immediate question arises: Is there a sensory system that utilizes the information pattern, as such, from several neurons to give the perceived aspects of the sense? Such a system is shown in FIGURE 2. Two neurons may present four feelings, $2^2=4$; nothing, warm, cold, and hot. This analysis can be demonstrated experimentally by running warm water (40–44°C.) through one coiled tube and cold water (0–5°C.) through another coaxial tube, as shown in the illustration. On gripping the coils in the hand one experiences a *hot*, burning sensation while, in fact, only *warm* and *cold* have been applied. While the behavioral properties of this system are clearly perceived, the neurological discriminating centers have apparently not yet been found.

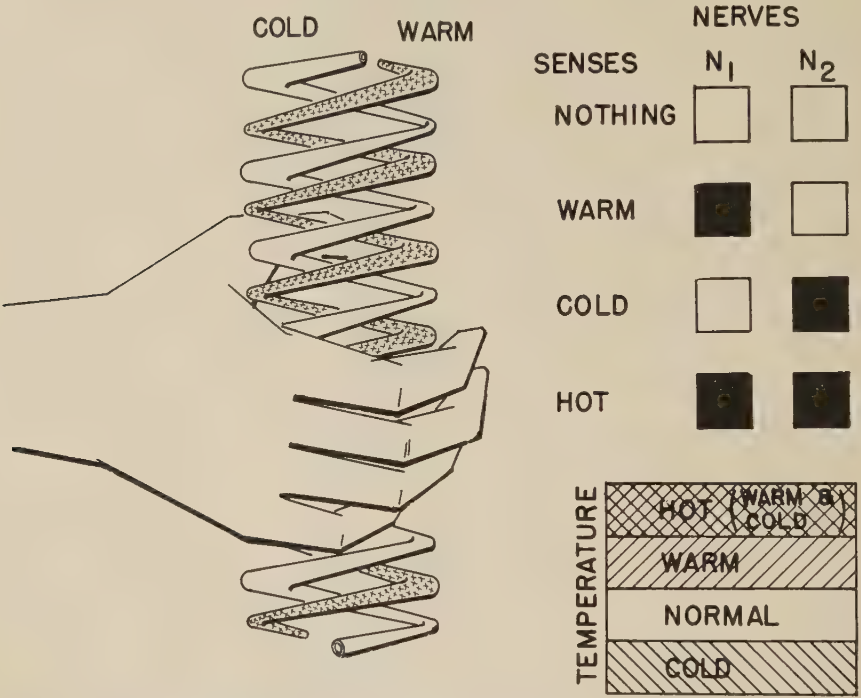

FIGURE 2. The configurational aspects of the perception of temperature. Two neurons, by their patterns of activity, can represent four sensations: nothing, warm, cold, and hot. The stimulation of hot can be demonstrated experimentally by circulating cold water (0–5° C.) through one coil and warm water (40–44° C.) through another intertwining coaxial coil; thus cold plus warm equals hot.

If we assume that there are at least 10,000 known odors, then $2^N =$

10,000, where N is the number of neurons which must operate in parallel for 10,000 different patterns; in this case, N is greater than 13. Now, the receptor mechanisms may not allow utilization of all the communication patterns, so that N must be greater than 13 and may be perhaps as large as 20 to give a capacity for digital patterns as large as the known number of odorants. Since we find that 24 mitral cells, or cerebral neurons, lead out of each glomerulus, 24 has been chosen as the number. In consequence, more than 16,000,000 patterns or odors are possible if the receptors, or end organs, have equivalent chemical discrimination. A board of 24 lights will give more than 16,000,000 patterns or configurations of lights if all possibilities are enumerated.

The use of parallel sheathed neuron channels to represent an odor immediately runs into a neurophysiological difficulty. With the neuron pulse duration only about 1/50 of the recovery time, the pulses that make up the pattern must be carefully timed. The "board" of 24 lights must not flicker or quaver but, to achieve 16,000,000 patterns, all the required positions must light simultaneously. Our difficulty is that the molecular collisions at the end organs are random in time. We must, therefore, find some timing or phasing device in the system to cause it to function in unison or to allow the discharge of the configurational response in all cooperating neurons simultaneously.

What is required is a short memory, or holding, function that takes the pulses roughly within an interval of 1/30 to 1/50 of a second and, at a signal, discharges the retained pulses. This function is in the manner of the starting gate at a horse race. The horses enter independently during an interval and are released on a signal. This phasing, or synchronization, is required for the transfer of configurational or digital information in the cerebrum.

Close examination of the neurophysiology reveals that a so-called "granular cell"[16,3,11] is in just the right place to serve this function. This cell is so small that its properties have not been observed and its function has not been characterized. We, therefore, postulate that it receives the pulse from the end organ, delays it until just the right time, and releases it; it serves as a modified memory cell. The interesting fact is that the olfactory bulb is known to pulse or mechanically fluctuate rapidly.[11]

Granular cells are reported in other places in the nervous system. For example, there are very large layers of granular cells in the cerebrum whose function is not known. These may be the fundamental digital storage cells of the cerebrum.

The question may be raised: Where does the timing signal come from? It is interesting to recall that there are basic electrical rhythms in the cerebrum. Also, continuous waves accompanying olfactory stimulation have to 60,[11] and 28 to 32 cycles[17] per second, respectively. Furthermore, been observed in the surface of the bulb both in the rabbit and man, of 55 Adrian[11] has recorded that, in a rabbit under sufficient stimulation, pulses from the mitral cells are synchronized with the surface waves.

If synchronized parallel channels of neurons are the information carriers in the cerebrum, there should be recognizable diseases for simple failures in this system. For example, epilepsy is characterized and diagnosed by the complete modification of these fundamental and normal rhythm patterns; the function of synchronism appears to have broken down. In neurosclerosis, the myelin sheath of certain neurons is attacked; and it may be speculated that, in scarred tissue, the transmission velocity of certain pathways is changed and that of others is not. The result is that a digital configuration transmitted at the synapses of a set of transmitting neurons does not propagate at equivalent velocity among the members of the group and, therefore, does not arrive in step at the endings. Thus, one pattern may be transformed to another pattern with attendant confusion.

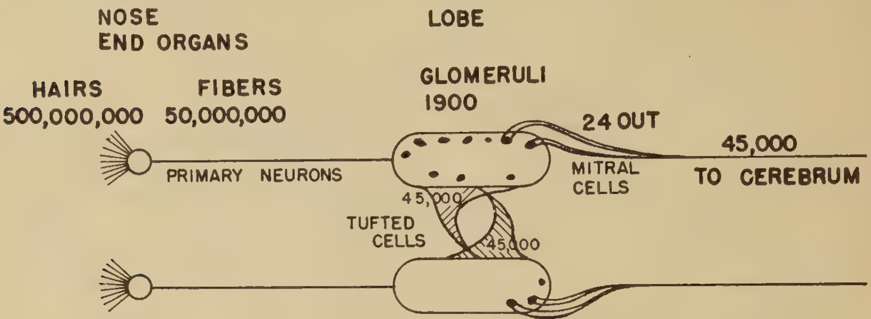

FIGURE 3. Summary of numbers of important elements in the olfactory system.

One problem yet remains: How is odor identification achieved at threshold for detection? Or how do we discriminate against meaningless response of "noise" pulses? As described above, there is an extra set of cells, including granular cells, in the form of a feed-back loop in the olfactory lobe from a mitral cell to a prior level, possibly on the same pathway, possibly on an equivalent pathway. In addition, the existence of a so-called two-junction synapse was indicated. To be brief, we suggest that the time sequence of pulses from a set of equivalent end organs reliably indicates the presence of an odorant only if pulses occur one after another in a train. This is consistent with Adrian's observations of the difference between stimulated[11] and intrinsic activity in the bulb. Below threshold, spurious results would give only occasional pulses with intervals between. The feedback loop, therefore, makes possible the presentation at a two-junction synapse of the time sequence of the information from the end organs as it comes, and of the same sequence delayed several time intervals. If pulses are present from both channels at once, a reliable response is indicated; if only occasional pulses occur, the signal is not reliable, and nothing gets through to the brain. Thus a satisfactory reliability mechanism explains the observed property that there is no consistent perceived response prior to identification.

A Model for the Intensity of Olfactory Response

We have outlined a system for differentiating quality; what type of model can represent the observed properties of intensity? The number of neurons

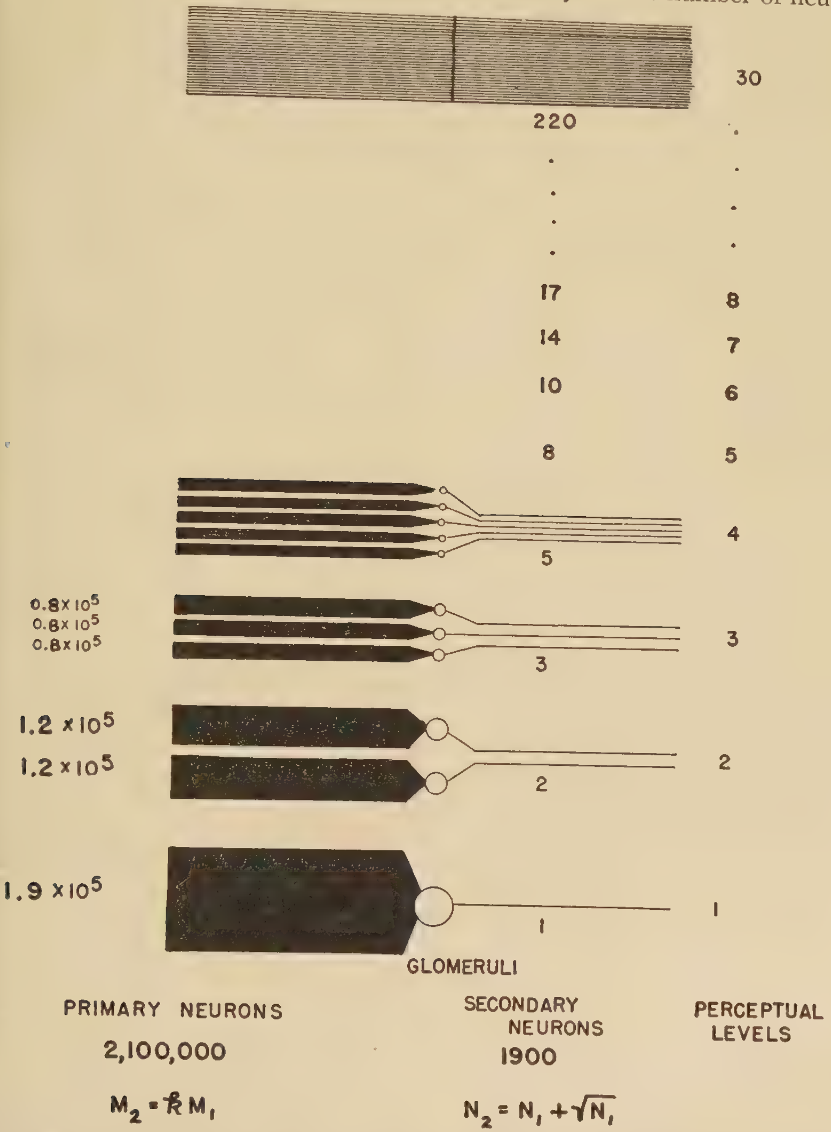

FIGURE 4. Theoretical model for the organization of the connections between the primary and condary olfactory neurons. From the number of primary neurons, the number of secondary neurons, e law of statistical fluctuation, and the Weber-Fechner law, three deductions result: (1) there are perceptual levels of intensity; (2) the effective concentration range for perception is 190,000 mes the threshold for identification; and (3) a 52 per cent increase in concentration is required for "just noticeable difference."

in the olfactory system was given above and is summarized in FIGURE 3. There are 50,000,000 primary neurons from receptors to lobe or bulb, and 45,000 secondary neurons from bulb to cerebrum. If we assume 24 different kinds of end organs, this gives 2,100,000 input and 1900 output neurons for each digit of the configuration. The perception of intensity must be proportional to the number of these 1900 equivalent neurons which are activated at a particular moment. The model for this intensity system does not connect the same number of primary neurons to each secondary neuron but, by contrast, connects as many as 190,000 primary neurons to but one secondary neuron and as few as one primary to one secondary neuron. FIGURE 4, in part, pictures the way in which primary neurons may be connected to secondary neurons in our model. Using the above two numbers of input and output neurons, we can develop a system which explains the behavioral properties of the perception of intensity.

The law governing the perception of a "just noticeable difference," a JND, should be a statistical law because the end organ-molecular collision is a random process over equivalent sites. The normal, or Gaussian, distribution law states that, if we are observing the statistical activation of, for example, 100 neurons, the fluctuations will be $\pm \sqrt{100} = 10$. Therefore, to indicate that there is an increased external signal, the number of neurons responding must be increased by greater than the square root of N. Thus, we obtain a formula for the numbers of active neurons associated with two adjacent perceptual levels:

$$N_2 = N_1 + \sqrt{N_1} \tag{1}$$

A recursion formula of this type can be used to describe the perceptual aspects of intensity if the groups so defined are active essentially only one at a time. This will be true if a saturation phenomenon blocks the overstimulated pathways. If we apply this rule on the cerebral side of the bulb to the secondary neurons, beginning with one neuron in the lowest group and continuing until all 1900 neurons are assigned, we obtain 30 groups or perceptual levels.

On the receptor side of the bulb, an entirely different rule of organization applies, which has to be devised so that the Weber-Fechner law is satisfied. This law can be stated in the form:

$$\frac{C}{C_0} = k^{\mathrm{JND}} \tag{2}$$

where C is the external concentration within the perceptual range, C_0 the concentration for the identification threshold, JND the number of "just noticeable differences" above threshold and k the constant representing the ratio of concentrations for one JND. The external concentration corresponding to two adjacent intensity ratio levels can, therefore, be written as

$$\frac{C_2}{C_1} = k. \tag{3}$$

We now assume, as properties of the olfactory system: (1) that the activity in the primary neurons is directly proportional to the external concentration of the odorant; (2) that if M primary neurons are combined in the bulb into one secondary neuron, the pulse rate in the latter is proportional to M times the primary activity; (3) that there is a maximum pulse rate in the secondary neurons. Now, if the secondary neurons in one intensity group are each connected to M_1 primary neurons, then

$$\frac{M_2}{M_1} = \frac{C_2}{C_1} . \tag{4}$$

Hence, combining EQUATIONS 3 and 4, we obtain the following simple organization rule for the primary neurons,

$$M_2 = kM_1 . \tag{5}$$

We now have to assign the 2,100,000 primary neurons to the thirty intensity levels using the recursion formula, EQUATION 5. This time, we start with $M = 1$ at the highest level, meaning that we connect one primary neuron to each of the 220 secondary neurons in that level. It turns out that the value of k must be 1.52 in order to use up all the primary neurons when the lowest level is reached. Under these conditions, the number of primary neurons per secondary neuron in the lowest level is 190,000.

Thus, the condensation ratio varies by a factor of 190,000 from the lowest to the highest intensity level. The corresponding concentration C required to excite these levels must also, from EQUATION 4, vary by the same factor of 190,000 which is, therefore, the dynamic range of the system.

In summary, FIGURE 4 shows the complete organization of these primary and secondary neurons. This system has been derived on the basis of the two physiological numbers, 2,100,000 primary neurons into the olfactory bulb and 1900 secondary neurons out of it, for each of the 24 receptor types, together with the law of statistical fluctuations and the logarithmic response law. From this, two independent theoretical constants have been deduced; the input concentration range of the system is 190,000, and the number of "just noticeable differences" of intensity is 29. These two numbers imply that the concentration ratio corresponding to one JND is 1.52 (that is, more than a 52 per cent increase is required to detect a difference), and also that the condensation ratio of primary to secondary neurons must vary from one to 190,000.

Let us compare these results with laboratory experiment. The data[18] for anethole are given in FIGURE 5. These data were obtained from a panel of seven people individually queried at three different times. Preliminary data established the 1 per cent solution to have an intensity of 3 on a subjective scale of 5 and subsequent judgments were conducted on that basis. The JND's were measured in the middle of the range by directly comparing, in rapid succession, two samples; these were progressively modified in concentration until the arbitrary criterion of 70 per cent correct identifications in 40 trials, or 65 per cent correct in 80 trials was met. Dividing the observed size of the JND into the intensity scale gives the total number of JND's.

The experimental data are: The concentration range is 200,000 ± 50 per cent; the constant k = 1.58 or 58 per cent increase is required to detect a difference; and, therefore, 26 ± 1 JND's are possible. Compare these with the theoretical values of 190,000, 1.52 or 52 per cent, and 29 JND's. In addition, the experimental data involved the arbitrary criterion of per cent correct, so that, as would be expected, the number of levels experienced is slightly less, not more, than the theory predicts.

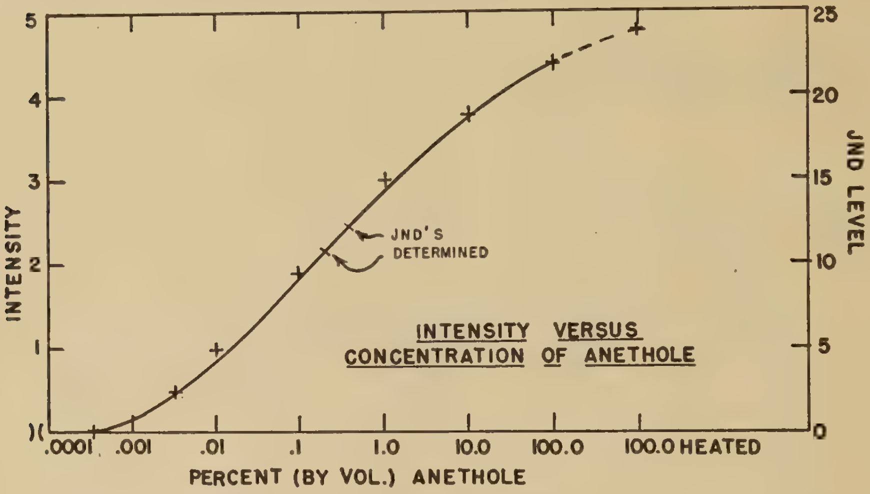

FIGURE 5. The experimental determination of the threshold, the range, and the size of a "just noticeable difference" for anethole diluted in mineral oil. The threshold for recognition is about 0.001 per cent; the maximum of the perceptual range is at a partial pressure greater than the vapor pressure at 25° C.; the range is, therefore, of the order of 200,000 times threshold. A "just noticeable difference" determined statistically in the middle of the range requires a 58 per cent increase in concentration. This results in 25 JND's.

All of these numbers are subject to some adjustment. The S-shaped tails of the intensity curve can be explained in the overlapping of secondary neuron response characteristics. The important feature is that for every animal there are three important constants: the absolute value of the threshold, the slope of the perception-concentration line, and the number of JND's in the concentration range for perception. The latter two numbers can probably be predicted from appropriate neuron counts. The former, however, requires detailed knowledge of the receptor mechanism.

This intensity analysis means that all odorants have the same number of JND's and the same size of JND, but the concentration scale may slide to account for the observed threshold.

Adaptation and Fatigue

Two important features of olfaction are adaptation and fatigue, both of which take place on continued exposure to constant, homogeneous odorants.

The sensation of an odorant on long inhalation diminishes both qualitatively and quantitatively. Similarly, an odor may be detected when one enters a room but later it becomes unrecognizable. This behavior is commonly called adaptation. The inability to detect concentrations near the threshold after exposure to very high concentrations may be called fatigue. The distinction between these two effects involves both time and concentration.

According to the proposed model, fatigue results from the slow recovery of the receptor processes and is important only after long exposure to relatively high concentrations. Adaptation, by contrast, takes place in the secondary neurons, probably in the olfactory bulb, and results from the temporary blocking of the afferent pathways as a consequence of continued stimulation.

A O X O X O X

B O X O X O O

C X O X O X O

D X X X X O O

FIGURE 6. Six digits of the 24-digit code which represents an odor. The codes as given can be used to explain the secondary behavior characteristics of masking, cancelling, enhancing, and anosmia.

This interpretation is not inconsistent with Adrian's results,[11] which suggest that adaptation is due to the partial reversion of the synchronized activity in the bulb to the unsynchronized, intrinsic activity of the bulb. The return to random or intrinsic activity may be taken as evidence for blocking in secondary neurons of the olfactory tract.

Fatigue can be avoided by eliminating high concentrations; adaptation can be avoided by the use of nonuniformly dispersed odorant mixtures or by the process of sniffing. Any osmoscope which employs homogeneous odorant-air mixtures is, therefore, subject to error from adaptation.

Application of the Olfactory Theory

This theory of olfaction has been constructed to lead to new predictable experimentation which can further the science and technology of olfaction. The applications of the theory are many and a few can be illustrated by using the symbols given in FIGURE 6. These symbols suggest the first six digits of the 24 digit olfactory code in the secondary neurons. X's imply pulses; O's, no pulses. Fatigue of the receptors, for example, of A, will also fatigue B but not C; it will change D. A will cancel C. A and D in subthreshold amounts will enhance the detection of B but not C. The loss of a digit from partial anosmia produces changes in some, but not in other, odorants. Careful observation at threshold may show that some digits are perceived perhaps at slightly lower concentrations than others and, therefore, slight changes on dilution are possible.

The method of classification of odor on the basis of this theory is to determine the interference at saturation and at threshold of various materials. For example, at saturation, fatiguing with a given odorant divides all other odorants into three classes: (1) those that are also fatigued have fewer of the same digits; (2) those that are unchanged have all different digits; and (3) those that are modified have mixed digits.

Similarly, for a given odorant at threshold, three kinds of response result from subthreshold additions of another odorant: (1) those odorants that reduce the threshold of the given odorant include all the digits of the given odorant; (2) those that do not change threshold concentration have all different digits; and (3) those that change the quality of the odorant very close to the threshold have some digits in common. The attendant changes in quality may actually require that a greater than normal concentration for threshold be present to produce a reliable identification.

These classification rules are very complex; they are not entirely satisfactory for organizing the empirical results and are remotely analogous to the deductive problems of genetics. The fact that the rules are complicated is another statement of the experimental fact that no wholly satisfactory classification system has heretofore been found. This is true because no classification system yet synthesized allows sufficient informational capacity for the data experienced. The natural modes of the system (that is, one pulse at a time in each of the 24 positions) are not perceived separately by the brain. Discrimination is made on the whole of the information experienced rather than on its individual components.

It may well turn out that one of the empirical classification systems, either measured descriptively or electrically, clearly indicates that in the perception of odor the learning process is of primary importance. Since an odor sensation cannot be recalled from memory but may only be recognized at the time of the experience, the memory clues on which improved discrimination is based must come from recalling the descriptive and qualitative aspects of the experience. Emphasis should, therefore, be placed on the dramatic or nostalgic aspects associated with olfactory stimulation and on the intuitively evident classes of odor (*e.g.*, fragrances) as aids to enhanced perception.

The applications of the intensity data, derived from the model, to many practical problems in olfaction are self-evident; *e.g.*, the application to deodorization. A major difficulty both in the work of a flavor panel and the quantitative application of its data has been the absence of a clear-cut model for what could be achieved in smelling. The informational emphasis on a digitally coded system of parallel neural channels leads directly to speculation concerning the cerebral functions of organization and memory, and to the Gestalt content of these processes.

An extension of this informational model to experimentation on the olfactory receptors has yet to be achieved experimentally. It should be interesting to attempt to count the number of specific end organ processes by enumerating the number of separately observed thresholds of identification to which the olfactory end organs respond.

The experimental testing of the olfactory model can be undertaken in several fields. The most important feature of the model is the digital patterns on 24 different parallel neural channels represented by 24 different end organs, respectively. Directly related is the phasing or synchronization of the secondary neurons observed by the careful work of Adrian. These properties, apparently, can be best evaluated by experimental neurophysiology.

There is much work to be done in establishing the threshold for identification, the perceptual range, and therefore, the size of the JND, for a wide variety of odorants. It is interesting to consider the testing of the proposed model by examining the growth of the nervous system, both in the development of the race and of the individual. A study to determine whether still other postulated neural networks are consistent with all the known data is highly desirable.

Finally, it would appear feasible to extend the analysis of olfaction to animals, including insects, which vary widely from mammals in olfaction, to clarify its function and to determine its informational content.

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Part III. The Status of Subjective and Objective Measurement Techniques

THE VALIDITY OF PRACTICAL ODOR MEASUREMENT METHODS

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Purpose

The ultimate purpose of our work is the development of new and the evaluation of extant deodorants for use in the air-conditioning field in an engineering manner. For such an application it is necessary to deal with the various phases of the subject, such as odor load, removal rate, initial and operating cost, and deodorant life, in other than abstract terms. Since odor concentrations cannot be put in fundamental increments as decibels for sound and lumens for light, a major hurdle in this work is one of odor measurement. In this paper, odor measurement methods and modifications for their use in application studies are described.

Introduction

Enough is recorded elsewhere in this monograph to establish that odor measurement, *per se,* does not exist. Universal units of odor and increments of intensity are still to be found. Yet, in many phases of odor studies, indicators of odor concentration are needed and are, in fact, available. The form these indicators take is shaped by the specific need. Therefore odor measurement must be discussed in terms of the over-all approach to the particular odor study.

Since its beginning, the air-conditioning industry has been using large amounts of outside air for the sole purpose of diluting odors and other internally produced contaminants. In the average installation 20–30 per cent, and in many installations 100 per cent, of the total air recirculated for cooling and dehumidification purposes is outside air. The reduction in first and operating cost, if the need for outside air were removed, is the objective. The monetary savings were discussed by Meek,[1] who showed a 20 per cent reduction in cooling costs and 45 per cent in heating costs if outside air quantities were drastically reduced. Ziel and Sleik recognized similar advantages.[2] The humanitarian service of an odorless air is immeasurable, whether one is concerned with aesthetic values only, or the improvement of health demonstrated by Winslow.[3]

The crux of the problem, however, is that the industry has an odor-control mechanism, outside makeup air. Any deorodant substituted for outside air must compare favorably from an economic standpoint to be worthy of consideration. No substitution of a deodorant for outside air can be made without this comparison. The deodorant must be a carefully engineered product, not a gadget whose sale depends on the whim of the public.

This substitution of an air-sanitizing agent for outside diluting air is by no means novel, with such terms as "air repair,"[4] "air recovery," and "air conservation"[5] appearing more and more frequently in the literature. It is stressed only that air heated, cooled, or dehumidified is not economically expendable simply because of its odorous contaminants.

There are three possibilities for odor control; the reducing of odor generating qualities of the odorant source, the neutralizing or masking of its effect, and the complete removal or destruction of the odor. Investigation of the first of these is under way at the American Society of Heating and Ventilating Engineers Laboratories.[6] While this information is of extreme value in the over-all picture of odor control mechanisms and while it will be of value on specific problems where there is a constant inanimate odor-generating source such as egg rooms, dairies, and others, the use of this technique is limited in human comfort air conditioning where the major odor source is directly or indirectly the occupants themselves. The use of maskers has more limited use. Dividing these into their three modes of activity, irritants, perfumes, and neutralizers, we concur with the National Bureau of Standards work by Weaver.[7] With the first, it is contrary to sound practice to destroy a God-given sense by irritating or anesthetizing agents which may do more physiologic harm than the esthetic or real harm of the odors themselves. Concerning perfumes, there is no such thing as a universally pleasant odor. In an unreported survey of human reaction to a highly perfumed commercial deodorant in 1944, we found that 15 per cent of the test subjects associated the aroma with a dentist's office, 25 per cent with a funeral parlor and only 60 per cent had pleasant associations. Our experiences with perfumed "deodorizers" since that time have been of similar nature. Toward odor neutralizers, the attitude is one of passive objection. The phenomenon as reported by Zwaardemaker[8] and many others is beyond question. A review of Backman's work,[9] however, will show the critical nature of concentrations involved. There are two apparently insurmountable aspects to this technique: one, the inability to vary properly the concentration of the neutralizer with variation of the concentration of the odor to be neutralized and, two, the inability to discover a neutralizer effective against the many odorous components found in, for example, tobacco, cooking, and body odors. Any unbalance in a neutralizing system will result in the appearance of the undesirable odor to be controlled or the odor of the neutralizer (usually pleasant) which would have the same disadvantages as the perfumes mentioned above.

The remaining possibility is that of odor removal or destruction. The ideal is that of destroying the odor at or near its point of origin, hence a gas. A search for gases with this property reveals none which are not equally destructive to human tissue, placing them in the irritant class above. It is necessary, therefore, to bring the odorous air to the deodorant mechanism and return the cleansed air to the contaminated space. This is a dilution phenomenon, the odor never being totally absent but kept at tolerable levels by continuous deodorization. The method is ideally suited to air-conditioning systems since large quantities of air are continuously recirculated for heating, cooling, and dehumidification purposes, the deodorant merely being substituted for outside ventilating air.

An engineering approach to this method demands certain pieces of information: (1) the odor load, which is the total odor which must be removed per operating cycle and dictates the basic cost of the deodorant mechanism; (2) the maximum odor level to be maintained, since the higher level this is, the less the volume of air to be carried to the deodorant; (3) the efficiency of the deodorant mechanism which will dictate the size of apparatus and the quantity of odorous air to be moved through it. It is apparent that all three requirements involve odor measurements. Odor measurement is duscussed only in so far as it applies to this over-all picture of dilution odor control in air-conditioned human comfort spaces.

Because the complexity of natural odors appears to preclude any objective method of determining the above and because analytical chemistry yields methods for the quantitation of traces of many odorous organic compounds, workers are often tempted to evaluate deodorants on the basis of synthetic odorants. Typical of this is work recently reported by Brocklehurst[10] in which a current deodorant was "proven" to have no deodorant properties because it did not remove or destroy methyl mercaptan. While we hold no brief for chlorophyll and its derivatives, this was an unfair test. Our initial efforts were in the same direction.

In our laboratory, an excellent deodorant was developed using butyl mercaptan as the test odor. When this deodorant was checked in a nonventilated practical system with tobacco smoke, it was found that, while the mercaptans present in tobacco disappeared, the system became foul from the build-up of the other odorous components which the deodorant would not attack. The deodorant was specific for mercaptans. Because the same specificity occurs if one uses odorous acids, bases, alcohols, aldehydes, or others as test odors, it becomes impossible to use any synthetic odor as characteristic of naturally occurring odors except in those rare cases, such as egg rooms, where one specific odor is the offender. Even the use of synthetics for screening of deodorants is open to question unless extreme care is exercised in their selection.

Because deodorant evaluation must be done on the basis of naturally occurring odors, a survey of the most chronic offenders in the field is necessary. In human comfort systems these are found to be, in order, tobacco, body, and cooking odors. In our work, effort was directed toward finding an indicator which would relate odor intensity, hence odor problem, to the quantity of the source. For example, in a given type installation, burning tobacco is the source of the odor problem. A given quantity of tobacco burned will impart a certain quantity of odor to the air. A certain level (in unknown units) of this odor is tolerable by people; an excess of this level is not. Taking a given installation of known size, occupancy, and smoking rate, at what rate must the odor from the tobacco burned be destroyed by a deodorant or diluted by outside air to prevent the odor from exceeding the maximum tolerable level? This is dealing with the odor problem in the same manner as a heat source is considered in the air-conditioning industry. In engineering a job, the heat leakage of an individual window (metaphorically equivalent to the quantity of tobacco burned) is calculated. The size of the refrigeration plant, including the quantity of air to be recirculated (equivalent to the deodorant system), will be a predictable function of the number of these windows of known heat leakage. The only difference is that the odor researcher has no thermometer for initially checking the odor load of the space, the efficiency of his deodorant plant, or the final odor balance in the space. More than that, he cannot design a thermometer, because he does not know with what physical, chemical, or electrical portion of this vapor, registered as odor, he is concerned.

In the absence of knowledge of what terms, odor, and odor intensities will finally be found, it is necessary to treat each odor source as an individual problem. Furthermore, odor intensities emanating from this source must be in terms relative to the quantity of the source. The procedures described below, therefore, had to be directed toward the establishment of the problem in terms of the known and reproducible base, the odor source. Problems in other than recirculating human comfort systems might or might not yield to a similar approach.

Experimental Procedure

Fundamentally there are only two workable methods of odor measurement, the organoleptic and the chemical.[11,12] The densitometers, refractometers, and conductivity meters touched on by Doctor Greenspan were considered and found to be either unreliable or too insensitive.

Dilution Measurement. Since all work on the removal of odors must, in the final analysis, be put in terms of human sensibilities, attention was directed toward the dilution-threshold method. Because the olfactory threshold is the minimum concentration of an odor which can be smelled and because increases in concentration above this minimum cannot be evaluated by the unaided nose (Weber-Fechner law), this technique reduces all odorous air to threshold values. By mixing sufficient uncontaminated air to a measured quantity of odorous air, the odor present in the mixture is reduced to threshold.

This procedure is by no means new, the first device being the Olfactometer of Zwaardemaker in 1895.[8] This was simply two telescoping tubes, the inside of the outer being coated with the odorous material under test; the inner tube being inserted into the nostrils for sniffing. As the tubes were extended, more of the air being sniffed would come in contact with the odorous material, the odor concentration thereby becoming higher. By placing markings on the tubes, the amount of exposed surface of the odorant at the point of minimum detectable level could be recorded. Arbitrary values such as "olfacties" could be assigned and the relative intensities of various odorous chemicals could be compared. On the same order, van Dam[13] in 1917 used the same principle but sniffed through the outer tube, a center rod being coated with the odor. The degree of insertion of this rod at the point of threshold stimulation was also recorded in arbitrary units. More reliable apparatuses have been used by Hofmann and Kohlrausch[14] and Elsberg[15] for the same purpose, their improvements being the actual measurement of air and odor quantities and eliminating the use of sniffing as the motive force for creating the mixture of odor and air. These are, of course, all tools for studying olfactory function and are inapplicable to the determination of odor levels in application studies. They did establish, however, the dilution principle for odor measurement.

The first of consequence, and by far the best known, of the dilution systems for measuring of odorous concentrations of other than synthetic odorants is the Fair and Wells Osmoscope.[16] This was again two snugly fitting telescoping tubes, both containing banks of holes. In its most common usage, the inner tube is inserted into a flask containing the odorous liquid to be tested, the outer is inserted into the nostrils. As the tubes are extended, more diluting air is admitted by banks of holes. The number of times an odor must be diluted to reach threshold is recorded. For quality control this has found wide application in the perfumery, water supply, and sewage disposal industries.[17 21] It has had some application in determining odor levels in air but has two distinct disadvantages. It uses the operator's sniffing as the means of moving the air from the test chamber to the nose with the result that the exact quantities of odorous and diluting air are not known. Secondly, there is no control over the quality of the diluting air.

Of the apparatuses used specifically for measurement of odor levels in air, the Oronite Odorometer[22] for determining levels of odorants in gas and the Osmo of Proctor & Gamble[23] for evaluating plant odor problems are the most recent. Actually there is little to pick and choose among these or others which one may design. The measuring of air flows is the biggest single variable. As, for example, the Odorometer uses a fixed orifice and rotameter combined. The Osmo used a series of fixed orifices, so that the same baffle exposing additional orifices for the entrance of odorous air will close orifices to the entrance of diluting air.

With the understanding that the method of metering the air, the type of blower for moving the air and the throttling devices, is a matter of choice, FIGURE 1, which is a line diagram of our own device, illustrates the principle. The odorous air is drawn from test area through tubing A by blower B. This air quantity is measured by rotameter C. The odorous air passes to mixing chamber D where it is mixed with the purified dilution air. Dilution air is supplied by passing compressed air through a purifying train E for removing impurities. This air is then measured by rotameter F before entering mixing chamber D. The air mixture is discharged at sampling orifice G. The operator records the air flows at which the odor is just detectable at G. By proper balancing of air flows, this presents a method of reducing any concentrations of odor to terms of thresholds. For example, if 2 c.f.m. of purified air mixed with 1 c.f.m. odorous air renders the odor barely detectable, the odor in the original air was at a concentration of three thresholds. This figure represents our laboratory model using rotameters because of the extreme range of thresholds to be measured (from 1.1 ± 3,000). In our field studies, where we rarely encounter thresholds over five, fixed orifices are used in place of rotameters because of the cost of the latter. Whether fixed orifices, rotameters, venturi meters, or other gas metering devices are used is a matter of individual preference.

One critical point overlooked in most, though not all, previous devices is the degree of cleanliness of the diluting air. In our very early studies, using outside air for dilution, we could not get consistent thresholds because of interference by the subthreshold presence of odorous contaminants. Since then, all of our diluting air has been purified by the system shown in FIGURE 2. Air at 300 pounds pressure was brought in at A through a Mandler bacteriological filter B, a packed wool filter C, and an activated carbon cylinder D, the latter two being surrounded with solidified carbon dioxide. The air was then discharged through tube E to the apparatus. This has completely eliminated interfering contaminants. The Osmo also

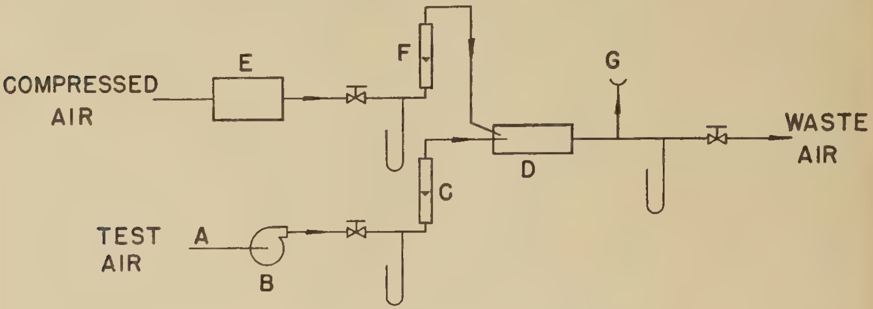

FIGURE 1. Dilution system to measure thresholds.

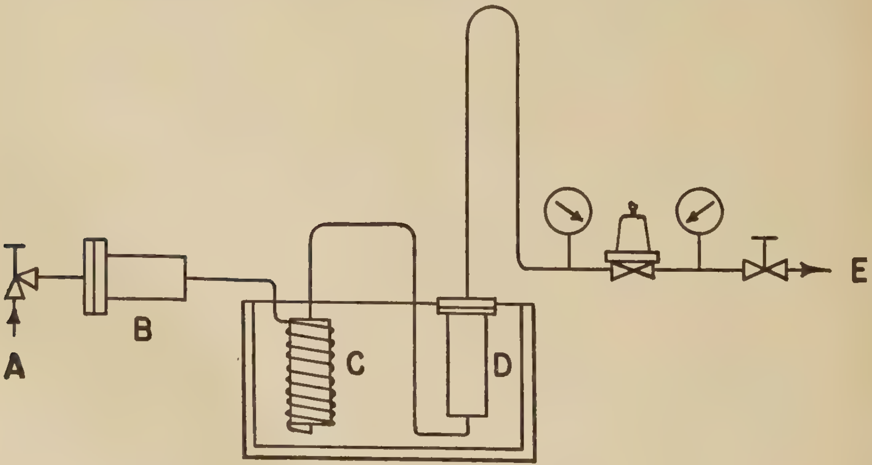

FIGURE 2. Air purification apparatus.

recognized this need but used activated carbon without pressure or refrigeration. This we found insufficient.

Because of its dependence on the sense of smell, this dilution technique, uncontrolled, is valueless in controlled odor studies. The extreme variation of sensitivity within an individual makes it impossible for an operator to take odor measurements over a period of time without knowledge of the level of his sensitivity at the time of sampling. One breath of ammonia can reduce an operator's sensitivity by 50 per cent for a 24-hour period. At the onset of a head cold, an operator's sensitivity increases strikingly before it is destroyed by mucous accumulation. Excessive drinking or smoking markedly reduces sensitivity temporarily. Additionally, the measured odor levels of one operator do not necessarily compare with those of another so that the same experiment run by two different operators would not necessarily yield the same results.

For standardizing the operator, several techniques have been devised. In surveying a large group of operators for this work, while extreme variation in individual sensitivity was found, two operators were found to have practically identical sensitivities to tobacco odors, cooking odors, and certain synthetic odors. Since it is unlikely that the sensory perception of two individuals varies simultaneously from physiological causes, two such operators serve as a control for each other. During test runs, when the readings of the two coincide, the data is considered valid; when the readings are divergent, the data are discarded. It has been found that in almost 100 per cent of such readings over a four-year period, the two operators confirmed each other so that reports of variation of the human sense of smell appear to be exaggerated.

The possibility still remains that two such operators could vary simultaneously under certain circumstances. To guard against this, another technique was found suitable for establishing absolute baseline of sensitivity. This involves the dilution measurement of a constant known odorant to determine the per cent efficiency of the nose at any time during a series of experiments. In a closed vessel, a liquid will saturate the air above it to a concentration governed by its vapor pressure, temperature, and pressure. This will be an unvarying concentration so that the dilution-threshold measurement of concentration of an odorous liquid by a given operator will always be the same, provided the sensitivity of his nose does not vary. Any variation in the sensitivity of the nose will be reflected in a higher or lower threshold reading for the invariable vapor concentration. In an air-tight container, xylene was permitted to permeate the air to saturation under controlled temperature and pressure conditions. In a prolonged series of experiments, the normal odor level of xylene was found to be 380 thresholds. If, on a given day, an operator found xylene threshold values greater or less than 380, his per cent efficiency could be calculated and his test data corrected accordingly. Divergent readings of two operators can be corrected in a similar manner. This has been repeated for other odorants trying to get closer to the type of odors with which we are concerned. Among these, nicotine is typical. At standard temperature and pressure, nicotine saturates air to 3,000 thresholds at our operators' senstivities. This requires too cumbersome dilution apparatus so we have stuck to the less intense odors.

A third method is to define the operator's threshold by the source producing this threshold. Such as, for our operators, 0.001 gm. of tobacco burned per cubic foot of air equals one threshold. Any reporting of threshold data must define the experimenter's sensitivity in these or similar terms. In the final analysis, this is a must for the actual comparison of the work of different experimenters.

Chemical Measurement. Because the odor of burning tobacco is a complex of a great many odors, the majority of them unidentified, an objective indicator of relation between the odor level and the quantity of tobacco burned seems remote. The two apparent methods are that of measuring only one chemical in the complex and using that concentration as an indicator of the quantity of the whole. The other is to find some general overall characteristic which is reproducible and proportional to the quantity of tobacco burned.

While the effort to find reproducible concentrations of individual odors in tobacco smoke failed, it was found that certain oxidants react with odor complexes in a reproducible manner. This is not original; the Lang, Farber, and Yerman "Stinkometer"[24] employs this principle to determine the state of freshness of certain foods by reacting the vapors exuded with certain oxidants. In a search for similar oxidants for our use, one in particular was completely interreactible with tobacco and cooking odors. During this reaction, the oxidant is reduced and the odors destroyed. The amount of reduction is measurable and directly proportional to the quantity of tobacco burned or food cooked.

Three major systems were used in the chemical study of tobacco smoke characteristics. While in earlier studies, these systems were distinct and separate, their principles are discussed in terms of FIGURE 3, which is a composite of all three. In the first studies, tobacco was burned in the pipe in the presence of purified air at various flow rates measured by rotameter C. All of the tobacco smoke passed through the mixing chamber D and absorption train A, train B being eliminated from the system by valves. (The absorption trains are a series of 1.5 inch tubes, each tube containing an oxidant with which the odorous air is brought in intimate contact by gas dispersion tips). The results were recorded in terms of quantity of oxidant reduced per weight of tobacco burned. When studying the effects of dilution on tobacco odor, quantities of purified air, measured by rotameter E, were passed into the mixing chamber D, together with odorous air from the pipe. Portions of this air passed through train A and the remainder was discharged to waste F.

Since we have long since established the validity of oxidants as indicators of odor concentration, we are currently using the apparatus as sketched on FIGURE 3 for the screening of deodorant chemicals. For measuring deodorant abilities, equal portions of diluted odorous air are distributed to each of the two trains, A and B. In train B the odorous air passes directly into two tubes, B-1 and B-2, containing the oxidant for measuring the quantity of odor present in the original air. In train A, the odorous air passes through the deodorant mechanism under test (A-1 and A-2) before passing through the oxidant mechanism tubes (A-3 and A-4). This measures the quantity of odor left in the air stream after subjecting it to the deodorant. A comparison of the quantity of oxidant reduced in each of the two legs indicates the efficiency of the deodorant. In addition, it permits the prediction of cost of a deodorant mechanism for any size odor load.

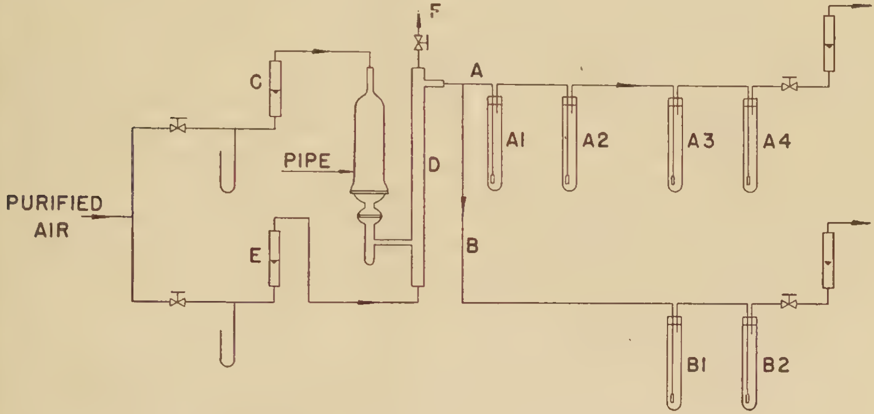

Figure 3. Absorption system used in chemical measurement of odors.

Experimental Results

Using the oxidant train, quantitative measurements of the odorous components of tobacco smoke were determined (TABLE 1). In these tests, four rates of combustion were used; the slowest approximating the smoldering rate and the most rapid approximating the puffing rate of natural smoking. In conditions 1 and 2, all of the odor produced by the complete burning of the cigarette was collected in the absorption train. In conditions 3 and 4, the odorous air was diluted 30 times by purified air and only 1/100 of the

Table 1
Quantity of Oxidant Reduced by the Vapors of Burning Tobacco

Condition	*Burning Time 1 cigarette*	*ml N/10 Oxidant Reduced per gram Tobacco Burned*
1. Total Absorption	15 minutes	120
2. Total Absorption	35 minutes	125
3. Dilution Partial Sampling	18 minutes	118
4. Dilution Partial Sampling	.5 – 1 minute	117

total mixture passed through the absorption train. In these tests various quantities of name cigarettes, both fresh and stale, were used.

In all cases, the results were strikingly similar, as recorded in TABLE 1 which is a composite of 200 tests. There is close uniformity in odor production by cigarette tobacco regardless of brand, degree of freshness, and rate of combustion, and this holds true even with extreme dilution of the odor. Artificial burning of tobacco, because it is reproducible, can, therefore, be used as a laboratory tool in the investigating of odors; and the variables mentioned, which would be expected in human smoking, need not be considered as interfering variables. Secondly, the oxidant is shown as valid for indicating the quantity of tobacco burned, hence the amount of odor produced.

It is recognized, of course, that an oxidant will react with all of the reducing components present in the tobacco smoke, many of which will be odorless. It has been established, however, that while an average of 120 ml. of the oxidant will be reduced by 1 gm. of tobacco mechanically burned, only 48 ml. or 40 per cent as much was reduced by the tobacco smoked by humans. When operating in practical rooms, it was found that while .01 gms. of tobacco human-smoked would yield 1 threshold to 10 cu. ft. of air, only .004 gms. mechanically smoked would yield the same odor level, the same 40 per cent relationship.

How neatly these pieces fit together will best be shown by presenting the results of selected deodorant testing. As mentioned earlier, the application is to be a recirculating-type system, odorous air being carried from the room to the deodorant and returned to the room partly freed of its odor load. Because the higher the concentration of odor, the greater the speed of reaction of the deodorant, and because the only odor the deodorant has to work on is that carried from occupied space, it is desirable to permit the odor level in the room to increase to the highest comfortable concentration.

To explore this, in a test using four subjects smoking at a controlled rate, without fresh air makeup or a deodorant mechanism, the odor in the test room builds up in regular steps to intolerable levels proportional to the quantity of tobacco smoked. There was a distinct relationship between the quantity of tobacco smoked, the threshold level, and the ml. of oxidant reduced. Repetition of the test with mechanical smoking yielded the 40 per cent relationship mentioned above.

In this test it was found that a group of assorted subjects, smokers and nonsmokers, recorded the room as immediately objectionable when concentrations of 2.5 and 3.5 thresholds were reached. In a room maintained at 2.0 thresholds, a similar group of subjects reported the condition distinctly bad after prolonged exposure. It has been established the tobacco odor in any room should be held at or below 1.3 thresholds. This would be the only odor the deodorant could work upon. With a fixed odor load, the volume of air required to be passed through the deodorant would be dictated by the efficiency of the deodorant.

This is illustrated by a series of experiments run in office spaces. The occupancy was four men, each smoking one-half pack of cigarettes per eight hour day, or 3.3 gm. tobacco per hour (mechanical smoking at 1.3 gm./hr. was also used). Within less than one hour, the threshold would rise to objectionable levels of 1.9 thresholds; exceeding the desirable 1.3. Once the threshold level had reached 1.3, odor had to be removed from the air at the rate of 3.3 gms. tobacco burned odor per hour. Since the only odor which could be removed was that carried to the deodorant at a concentration of 1.3 thresholds, the quantity of air to be recirculated depended upon the efficiency of the deodorant. It was impossible to find a 100 per cent efficient deodorant, but substituting outside air for a deodorant (equivalent to a reduction of 1.3 to 0 per pass), the outside air required was 42 c.f.m. In pursuing these tests with deodorants less than 100 per cent efficient, one which would reduce the odor level in recirculated air from 1.3 to 0.5 thresholds per pass through the deodorant, would require the recirculation of 69 c.f.m and one reducing from 1.3 to 0.7 would require 90 c.f.m.

By knowing occupancy, smoking rate, and deodorant efficiency, the specifications for any size of installation can be predicted. The validity of this method has been established in plants ranging in size from 60 to 6000 c.f.m. and for occupancies of from 2 to 500 people.

Summary

It has been pointed out that odor control is a real economic need in the air-conditioning industry; that the satisfying of this need is the substitution of deodorant mechanisms for outside air. This substitution cannot take place without a comparison of the abilities of deodorants in other than subjective terms. This means measurements of odor intensities. Since there is no universal odor unit, however, an all-inclusive odor measurement method is impossible. It becomes necessary to work with the available tools and so relate the results to reproducible standards as to make the results valid.

An approach to deodorization, as such, in the air-conditioning field is discussed. It is shown that to satisfy the requirements on this application, studies must involve natural odors rather than synthetic odorants even though the handling of the latter is much easier.

The two known methods of measuring odors (organaleptic and chemical) are discussed. By both of these techniques the odor level in air can be reproducibly determined in terms of the quantity of odor source. No claims are made as to odor levels in terms of absolute physiological or psychological values; the ignorance of what these units may eventually be is stressed.

Even though such studies must involve naturally occurring odor complexes, the control of such odors as burning tobacco, and cooking odors, is possible. Concentrations of tobacco odor are uniform and measurable and, therefore, the deodorant effect of any chemical or mechanism can be quickly evaluated from the standpoint of efficiency, cost, and other limiting factors.

By the dilution-threshold method, odor results in a practical plant can be evaluated. By the establishment of odor loads, desirable odor levels, and

odor removal efficiencies, the requirements of a deodorant are clarified and means for satisfying these requirements are given. It permits the solution of odor problems in an engineering manner and presents bases from which to specify for any installation.

It is suggested that while the over-all approach and the techniques were devised specifically for the problems of recirculating-type human comfort systems, they might find application, with or without modification, in other fields of odor investigation.

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SCHEME FOR ODOR IDENTIFICATION WITH EXAMPLES OF ITS USE

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Introduction

The examination of materials through sensory response is usually thought of as primarily concerned with food products. While much of the fundamental research has been done in this connection, the methods are applicable to the evaluation of most consumer goods. Moreover, the same techniques may be utilized in investigating problems of odor contamination of space and nonfood consumer items.

The absorption of foreign odors may not only cause consumer rejection of products but, in addition, the space odors may seriously affect the comfort of the occupants of public buildings, business places, or homes. Thus, the problems of odor identification and control are of vital interest to the owner of warehouses, restaurants, office buildings, theaters, stores, apartment buildings, and factories, as well as to the manufacturer of consumer items.

Many odor problems have been solved through the use of soundly devised organoleptic studies. While the techniques employed may vary according to the problem involved, there are certain principles of procedure which should be followed to insure reproducible and reliable results:

1. Selection and training of panel members.
2. Use of reference standards.
3. Control of test conditions to minimize bias and error.
4. Statistical analysis of results.

Scope of Odor Studies

The organoleptic study of odors includes description, identification, evaluation, and determination of the source of odors. Usually the problem is one of odor contamination, but it may also be one of development of a desirable odor either in space or in consumer goods. Thus, it may involve evaluation of masking odors, deodorization by absorption, elimination of the odor source, or blending of odors to make consumer products more acceptable. Whatever the problem, it has been our experience that the following scheme for odor studies has been applicable.

Scheme for Odor Identification

(1). *What is the problem?* As with any scientific study, a clear statement of the problem is required. This may appear quite elementary. With odor problems, however, obtaining a clear-cut definition is not so simple as it may appear. We have found that odor evaluation in the field is primarily a job for the detective. The detective work starts with obtaining a clear definition of the problem, often from persons who are not technically trained or who do not have a complete understanding of the factors involved.

(2). *What are the known and alleged facts?* Information regarding the following factors should be obtained.

(a) History of the problem.

(b) Description of the odor, whether it be a contaminant or a desirable odor.

(c) Description of the variations in odor character and intensity.

(d) Facts regarding probable cause.

(e) For problems of odor improvement, predictions as to probable consumer response.

All facts collected must then be classified as to which are known and which are only alleged to be true.

(3). *Preliminary Investigation.* (a) Examination, by one or more experts, of the premises or materials involved. This should include investigation of the facts, both known and alleged, in so far as possible.

(b) Review of the observations of the preliminary investigation and of facts, known or alleged, to make deductions as to probable cause, and to consider alternative causes which appear feasible.

(4). *Confirmatory Investigation.* (a) Field trips, using a trained panel of three or more experts.

(b) Careful panel check of deduced facts, using standard organoleptic procedures. This may include such techniques as triangular, duo-trio, rank order, or scoring of samples.

Preliminary Study of the Problem and Initial Investigations

Odor evaluation in the field is not only a job of sensory evaluation, but one of collecting facts and applying logic, intuition, psychology, and common sense. It is often necessary to obtain facts from nontechnical personnel who may respond to suggestions that certain odors are present when they are not, or who may give incorrect descriptions of odors which are present. While there are instances when prior information might bias results, most problems involving nonfood items are best solved when all facts are known. Once this information has been obtained, a preliminary investigation of the premises or materials is made by one or more experts.

We cite, for example, a complaint of a foreign odor in a business establishment which had become evident since the addition of an air-conditioning unit. Examination of the premises showed that vapors from carbon tetrachloride which was being used in a cleaning operation were accumulating in sufficient amounts to be hazardous. With the arrival of the air-conditioning unit, the windows were closed and ventilation curtailed. From the initial discussion, we could not be certain of the type of odor, nor could we determine whether the odor was produced by the air-conditioning unit or because of lack of ventilation. It was necessary for our experts to visit the establishment to determine the exact nature and cause of the odor. Thus, the problem was solved merely by a visit of competent odor experts. For other problems, the initial visit may be merely exploratory.

Where the source of odor contamination is suspected, the most effective approach is often prior examination of odorous materials which may have been the cause. We are aware that such practice might influence our examination. When trained experts make the evaluation, however, we have seldom found this to be true.

In one instance we were asked to visit a private dwelling to determine whether a foreign odor could have been caused by materials used for fumigation. Here, we first familiarized ourselves with materials which could have been used by the fumigator at the premises. We then visited the dwelling to study the odor present and also took a sample of air for chemical analysis. Additional evaluation of the odor characteristics of fumigants exposed to various conditions of temperature and humidity proved conclusively that the fumigants were not the cause of the unpleasant odor. In another instance, samples of fabric having an off-odor sufficiently strong for consumer rejection were claimed to have been spoiled during storage in a warehouse. We first visited the warehouse to acquaint ourselves with the odors which might be expected to be found in the cloth. Various samples of the fabric were examined for odor and portions of these samples were also evaluated after exposure to high temperature and humidity. It was found that the samples had odor characteristics which were not typical of fabrics, but were a blend of "fabric odor" plus a "pungent" odor which was present in the warehouse.

Sometimes the information presented during our initial conference can be misleading. In investigating the complaint of the presence of a foreign odor in a restaurant, the personnel disagreed as to its nature and its first occurence. Intensive questioning finally revealed that the restaurant had recently been renovated with new walls and ceilings, that an air-conditioning unit had been installed, and that some of the personnel were convinced that the odor was due to the air-conditioning unit. Previous experience with odors of this type, which we described as phenolic, led us to investigate the acoustical tile which had been installed in the ceiling. We also investigated the odors emitted by the air-conditioning unit. Confirmatory tests on a sample of the tile demonstrated the presence of a strong phenolic odor in the tile and a weak phenolic odor in the adhesive. With additional studies of air emitted from the air-conditioning unit, we were able to show that the tile was the cause of the phenolic odor in the restaurant.

Confirmatory Studies

After establishing, to some degree of certainty, the nature and probable cause of off-odors, confirmatory tests are conducted in the field or in the laboratory. A panel of three or more persons, usually five to ten experts, make the confirmatory studies. For these tests, standard organoleptic procedures are used.[4,6] These include selection and training of the panel members, use of reference standards, careful control of test conditions to minimize bias and error, and statistical analysis of results when necessary.

In setting up the panel, we utilize experienced panel members when possible. Most of us have some native ability to evaluate odor, but few are trained to use this ability to its fullest and to interpret our response accurately. To eliminate the possibility that an individual has a blind spot for evaluation of the particular odor under consideration, he is screened to test his ability, usually by use of the triangular test. If the problem involves very small differences, twice the number of persons expected to be used on the panel are screened by a series of tests, each succeeding test more difficult. This not only evaluates the ability to detect differences but also evaluates odor memory.

Training of the panel member, in many instances, occurs simultaneously with screening for selection. Training includes explanation of the method of evaluation, reasons for the study, discussion of the various odor notes to be considered, definition of terms, group discussions to clarify odor notes under consideration, as well as examination of samples which might be knowns or unknowns. Training continues throughout the entire program, and a constant surveillance of the panel members' performance is made.

Elimination of all variables which will bias the panel members' evaluation of samples is of primary importance. The samples must be coded so that their identities are unknown. Whenever available, reference standards are included for comparison. Such standards are required for most quality ratings. If possible, samples are placed in identical clean, odor-free containers. Generally, space odors cannot thus be handled. But materials which have been contaminated by space odors can be stored in suitable containers for evaluation. Concentrations of contaminants, masking odors, or desirable odors may be varied to show differences in odor notes. The samples can be exposed to various atmospheric conditions to accentuate odors.

The use of coded samples in space odor studies is demonstrated by evaluation of the odor emitted by paints as they are applied, or after drying. For this study, test chambers were built to simulate rooms, with proper attention given to the number of changes of air per hour and surface area per unit of volume. The panel members were given coded samples of paint to apply and were requested to evaluate the odor during application. The odor of the exhaust from each chamber, as well as the odor of the chambers, were evaluated during the course of drying.

For actual operation of the panel, the atmosphere should be free from interfering odors and the surroundings fairly quiet. The number of samples to be evaluated should be kept below the fatigue limit, as should the number of scoring sessions. This number is dependent upon the odors to be evaluated. It is seldom feasible, however, for one panel to handle more than eight samples per session and four sessions per day.

The primary consideration for each problem is selection of the method of evaluation. This involves the manner in which the samples should be treated, the reference samples required, and the experimental design which should be employed.

At our laboratories, we have found the triangular technique of evaluation most useful when samples are very similar. This involves presentation of each panel member with three samples, two that are alike and one that is different. He is requested to select the odd sample and, if possible, to state the reasons for his choice. Simple statistics can be applied to results of the triangular test.[7]

An example of the use of the triangular technique can be shown in a problem regarding off-flavor development in butter, allegedly due to waxed paperboard used in packaging. The board showed no objectionable odor when examined after aging at high humidity, or after soaking in hot water. Samples of fresh, lightly-salted butter were aged in contact with the waxed board at refrigerator temperature for as long as two months. These samples were compared, at weekly intervals, with samples of butter aged alone, using the triangular technique. The number of correct selections of the odd sample was not above the 33-1/3 per cent which can be obtained by chance alone. The waxed board was considered to be free from odors which would cause deleterious changes in the aroma and flavor of butter. Similar information could be obtained from a duo-trio test, where one sample is identified and must be matched with one of the other two samples submitted to the panel members. For this type of evaluation, however, the number of tests required is greater, since there is a 50 per cent probability of correct selection by chance alone.

For samples showing larger differences, rank-order studies, numerical scoring, or profile studies can be applied. If the question is one of strength of total odor, or strength of certain individual notes, or preference ratings, rank order studies are most applicable. This involves simply rating samples in order of strength of notes or preference. Simple statistics can be applied to the results.[1]

A modification of the rank-order method of analysis was used in a problem involving boxboard used for packaging cigarettes. The nature of the odor in the boxboard suggested a particular insecticide as the contaminant. Organoleptic comparison of the contaminated cartons with a series of samples of similar carton stock impregnated with increasing percentages of the suspected insecticide led not only to verification of the identity of the contaminant, but also to determination of the amount. This was the very low concentration of approximately 0.005 per cent, or 0.1 pound per ton of board. Correlation of this value with other available data indicated the probable source of contamination as some 2.5 to 5 ounces of the insecticide. The final conclusion was that a single paper bag in which this insecticide had been packed was accidentally present in the waste paper used for making the paperboard. In this particular instance, no known chemical methods would have permitted either verification of the presence of the particular insecticide or establishment of its concentration in the board.

Scoring various components numerically is somewhat more complicated, as it involves designing a scoring system, which includes determination of the proper weight to be given each factor under consideration. In a system which we have used for scoring many types of food products, we rate the perfect sample 100, assigning 30 points each to aroma and aftertaste and 40 points to flavor.[3] If odor alone is considered, the total of 100 points can still be assigned to the perfect sample, with decreasing ratings assigned according to the degree and type of off-odors.

A variation of this type of evaluation is the use of the profile method.[2,5] In addition to obtaining an over-all rating, it is possible to obtain a strength rating for each aroma note present. The profile method allows for pictorial presentation of the aroma and flavor. However, in our work we have found it effective to present results numerically in tabular form. The profile technique is applicable when a known standard of reference is available, or for comparison of differences between samples when no reference is available. Over-all quality ratings, obtained primarily when a reference standard is available, can be treated statistically, as can all numerical scoring systems. For our work, we usually use the standard errors of the mean values to estimate the significance of the differences among the samples tested.[4]

The profile method was used to solve a problem regarding contamination of a shipment of coffee. The odor predominant in the burlap bags was reminiscent of garlic. Our initial discussion and organoleptic investigation regarding this problem indicated that garlic was the cause. For verification, however, we considered asafetida and onion as possible causes. By profile analysis, samples of burlap impregnated with garlic, onion, and asafetida odors were examined in comparison with the sample in question. Examination of the odor profiles showed the sample in question was most similar to burlap impregnated with asafetida. Further investigation showed that the origin of shipment was an area where asafedita was one of the primary articles of commerce.

Many other problems have been successfully solved by our scheme of odor identification, such as selection of the most desirable of a number of samples of commercial alcohol on the basis of odor characteristics, determination of the source of odors in slippers where fire was alleged to be the cause, and solving problems of packaging in selection of the material that contributed the least odor. While we are aware that our scheme is based primarily on subjective olfactory response, and that objective methods are the goal of all odor research, at present there is no method which can replace sensory detection and evaluation of odors, whether objectionable or desirable.

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ODOROUS ATMOSPHERIC GASES AND VAPORS: PROPERTIES, COLLECTION, AND ANALYSIS

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Many practical odor problems, like those involving the tracing of odors to their sources and methods for odor control, must ultimately be solved by actual identification and isolation of chemical components for individual study. Much of our present information on constituents of common odors is purely nominal and based on old and incomplete research. To say, "body odor is butyric acid," or "cigarette odor is pyridine," is merely to use convenient abstractions for what are actually very complex and little-understood mixtures. Workers in other fields have faced parallel problems in which separation and analysis of chemical components were found to be important aids to understanding the properties of mixtures. For example, petroleum chemists have for some years appreciated the complexity of a mixture such as gasoline, and have devoted considerable efforts to its ultimate analysis and to detailed studies of the performance of its individual components.[5]

In this paper, the properties of atmospheric odorants and the relation of these properties to the problems of collection and analysis are critically reviewed. Methods of collection by sorption, condensation, and solution with and without chemical reaction are considered.

Properties

The extent to which a gas or vapor in the atmosphere is odorous depends on its prevailing concentration and its minimum detectable concentration (odor threshold). The prevailing concentration of an extraneous atmospheric gas or vapor depends, on the one hand, on its rate of generation (*i.e.,* its liberation into the air from sources such as human beings, animals, foods, tobacco, or chemical processes) and, on the other hand, on its rate of dilution by ventilation, of adsorption on solid surfaces, or of absorption by liquid or solid solvents.[21] Then,

$$C_w = G/Q_d$$

where C_w = Prevailing concentration of odorants (weight of odorants per unit volume of air),
G = Rate of generation of odorants (weight per unit time),
Q_d = Equivalent ventilation with odorant-free air (volume per unit time).

As previously implied, the odorous intensity of a gas or vapor is a function of the ratio of the prevailing to the threshold concentration:

$$\text{Odor intensity} = f(C_w/C_t) = f(G/Q_dC_t)$$

where C_t = threshold concentration of odorants.

---

* Present address: Tarrywile, Lake Road, Danbury, Connecticut.

TABLE 1
PROPERTIES OF ODORANTS

Lightest Odorant of Homologous Series		*Mol Wt.*	*B. pt. °C.*	*F. pt. °C.*	*Ordinary state*	*Vapor Pressure, mm. (a)*					
Series	*Compound*					*20°C.*	*Ice*	*NH_3*	*CO_2*	*CS_2*	*O_2*
Acetylene	Acetylene	26.0	−84.0	−81.8	vapor	43.1 atm	26.3 atm			67 (s)	<0.1 (s)
Acid	Formic acid	46.0	100.7	8.4	liquid	33	8.4 (s)	0.3 (s)			
Alcohol	Methanol	32.0	64.7	−97.8	liquid	96	30	2.7	0.1		
Aldehyde	Formaldehyde	30.0	−21.	−92.	vapor	(b)		392	22	1.0 (s)	
Alkyl halide	Methyl chloride	50.5	−24.2	−97.7	vapor	4.8 atm	2.5 atm	506	33	3 (s)	
Amine	Methyl amine	31.1	−6.5	−92.5	vapor	2.9 atm	1.3 atm	190	6.5	0.1 (s)	
Benzene	Benzene	78.1	80.1	5.5	liquid	75	25 (s)	1.4 (s)	<0.1 (s)		
Ester	Methyl formate	60.1	32.0	−99.8	liquid	476	195	30	0.7		
Ether	Dimethyl ether	46.1	−23.7	−138.5	vapor	4.95 atm	2.54 atm	496	34	1.5	
Ketone	Acetone	58.1	56.5	−94.6	liquid	177	67	8.4	0.2		
Mercaptan	Methyl mercaptan	48.1	6.8	−121	vapor	1.7 atm	577	109	3.8	0.1	
Olefin	Ethylene	28.0	−103.7	−169.4	gas	—	40.6 atm			462	0.1 (s)
Paraffin	Pentane	72.1	36.1	−129.7	liquid	427	185	31	0.8		
Other Odorants											
Ammonia		17.0	−33.4	−77.7	vapor	8.46 atm	4.2 atm	1 atm	44 (s)	0.6 (s)	
Arsine		77.9	−55	−113.5	vapor	15 atm	8.4 atm	2.8 atm	338	36	0.2
Carbon bisulfide		76.1	46.3	−111.8	liquid	295	127	21	0.6		
Chlorine		70.9	−33.8	−102	vapor	6.6 atm	3.7 atm	1 atm	62	2.5 (s)	
Hydrogen chloride		36.5	−84	−112	vapor	41.6 atm	25.5 atm	9 atm	1.3 atm	120	0.8
Hydrogen sulfide		34.1	−61.8	−82.9	vapor	17.7 atm	10.2 atm	3.6 atm	259	16 (s)	<0.1 (s)
Ozone		48	−112	−251	gas	—	—			1 atm	0.17
Sulfur dioxide		64.1	−10.0	−72.7	vapor	3.2 atm	1.5 atm	225	8.4 (s)		

(a) In mm. unless otherwise stated. Vapor pressures are referred to refrigerant temperatures of TABLE 4.
(b) Polymerizes to paraformaldehyde or α-trioxymethylene.

The rate of generation of odorous gases and vapors depends greatly on their volatilities at ordinary temperatures. It is, therefore, illuminating to examine the vapor pressures and other properties of the lightest odorous substance in each of the important homologous series of organic compounds (usually the first member) and of several other important atmospheric odorants. Such examination (see TABLE 1, columns 1–7, and FIGURE 1) reveals that the lightest odorous substances in each series are usually vapors or volatile liquids at ordinary temperatures, and that most of these are indeed the initial members of their respective series. Further, it is generally true that odor intensity increases with the ascent of a homologous series until opposed by decreased volatility.[15] Thus the properties of odorants imply that methods for their collection must be suitable for mixtures of widely varying molecular mobilities, chemical properties, and concentrations.

Collection

The fact that most indoor and almost all outdoor odorous atmospheres contain odorants in concentrations below 1 ppm. (by volume) makes it almost valueless to collect samples without concentrating them. Many excellent methods of collecting nonconcentrated gaseous atmospheric samples, such as the use of evacuated or collapsed containers, or gas or liquid displacement methods,[1,20,22] are suitable for collection only where one or a few gases in moderate concentrations are anticipated, or where the object of the analysis is to determine chemical functionality rather than identity. Complex mixtures of odorants can best be examined only after they have been isolated from the air, or at least considerably concentrated. The ensuing section considers the experimental techniques of preparing concentrated samples of atmospheric odorants.

General Precautions in Preparing Concentrated Samples. Whenever air to be sampled is conducted through equipment which continuously extracts a gas or vapor from it for analysis, it is essential to avoid any recirculation of such once-treated air through the extraction equipment. Therefore, the air which has passed through the equipment must be ejected into a space from which recycling is impossible. In outdoor air sampling, this is accomplished simply by exhausting downwind. In still air, the exhaust should be conducted by a tube or duct, or blown effectively away from the intake location. In addition, prefiltering to remove particulate matter and adequate metering of the total volume of sampled air are both essential. Where the filter for removing particulate matter becomes gradually clogged during the sampling procedure, so that its resistance continuously changes, the metering of the air must also be continuous or cumulative so as to obtain a true value of the total air volume sampled.

Collection by Adsorption. Any gas or vapor will, to some degree, adhere to any solid surface at ordinary or low temperatures. This phenomenon is called adsorption. Porous solids expose not only their exterior surface, but their interior surfaces as well, and some such solids, indeed, possess a vast network of extremely minute channels and submicroscopic pores within their

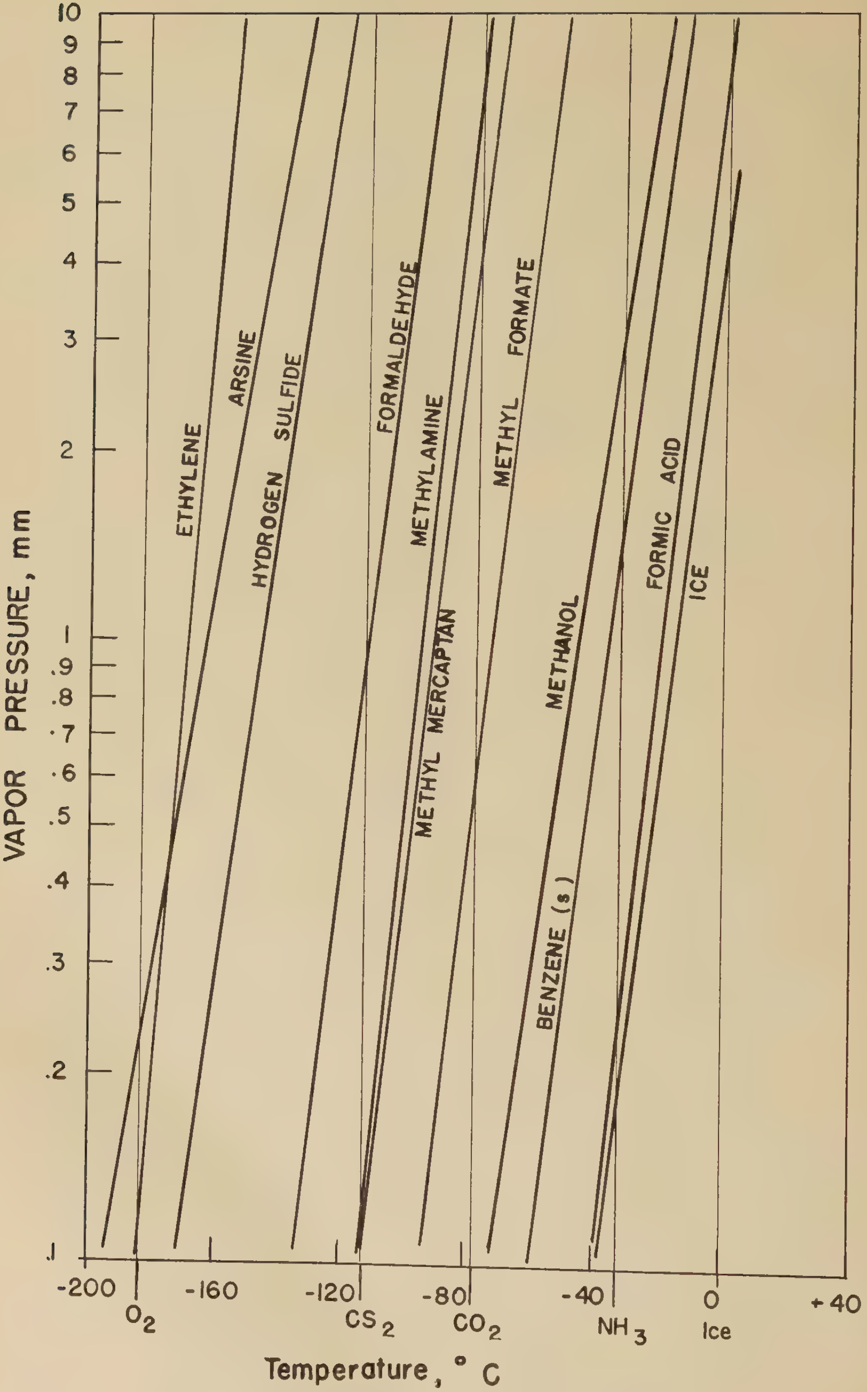

FIGURE 1. Vapor pressures of some light odorants.

body. Such materials have practical value as adsorbents. These solids include activated carbon, silica gel, activated alumina, and various active earths. All these differ widely in the number and kinds of substances they adsorb, as well as in the amount of sorbed substances they will retain. In general, the siliceous, metallic oxide, and active earth types of adsorbents are electrically polar; that is, their molecular structure contains an unsymmetrical electron distribution. Since polar substances have strong attraction for one another and since water is highly polar, polar adsorbents retain water in preference to most other vapors and are, therefore, incapable of adsorbing nonpolar gases (*e.g.*, many organic vapors) selectively from a humid atmosphere. For sampling odorants from ambient air, it is, therefore, most advisable to use activated carbon because this material is electrically nonpolar and is consequently capable of preferentially adsorbing organic material. In fact, previously adsorbed moisture will be displaced from the carbon surface as other gases and vapors are adsorbed, thus making it unnecessary to dehumidify the air prior to its passage through the carbon bed. Such prior dehumidification may even be undesirable because some of the gases and vapors to be collected may be lost in the dehumidification process.

To determine which gases and vapors may be sampled by physical adsorption using activated carbon, the following criteria may be used: true gases, usually having critical temperatures below —50°C. and boiling points below —150°C. are virtually nonadsorbable at ordinary temperatures by physical means. These include, for example, hydrogen, nitrogen, oxygen, carbon monoxide, and methane. Low boiling vapors having critical temperatures between approximately 0°C. and 150°C. and boiling points between —100°C. and 0°C. are moderately adsorbable. The adsorption efficiency at ordinary temperatures and concentrations, however, is not quantitative. Such vapors can be concentrated from the atmosphere by using a "thick carbon bed" (see below), preferably refrigerated. These vapors include ammonia, ethylene, formaldehyde, hydrogen chloride, and hydrogen sulfide. Chemisorption methods, elaborated below, may also be used for such low-boiling vapors. The heavier vapors (boiling above 0°C.) are readily adsorbed and retained by activated carbon at ordinary temperatures; these include most of the odorous organic and inorganic substances.

TABLE 2 gives minimum specifications for a gas adsorption activated car-

TABLE 2

SPECIFICATIONS FOR AIR PURIFICATION ACTIVATED CARBON

Property	*Specification*
Activity for CCl_4 *	At least 50%
Retentivity for CCl_4 †	At least 30%
Apparent density	At least 0.42 g./ml.
Hardness (ball abrasion) ‡	At least 80%
Mesh distribution	6-14 range (Tyler)

*Maximum saturation of carbon, at 20° C. and 760 mm., in an air stream equilibrated with CCl_4 at 0° C.

†Maximum weight of adsorbed CCl_4 retained by carbon on exposure to pure air at 20°C. and 760 mm.

‡Per cent of 6-8 mesh carbon which remains on a 14-mesh screen after vibrating with 30 steel balls of 0.25–0.37 in. diam. per 50 g. carbon, for 30 min.

bon which is suitable for physical adsorption of vapors as described in the preceding paragraph.

TABLE 3 gives retentivities of activated gas adsorbing carbon for representative gases and vapors. The retentivity is the maximum of a particular gas or vapor which the carbon will retain when exposed to uncontaminated air, and represents its *practical* sorption capacity for atmospheric collection.

To collect samples of vapors for which activated carbon has a retentivity of over 5 per cent (TABLE 3), a metered air stream is passed through a carbon bed of at least ¾ inch uniform thickness in the direction of air flow. The rate of air flow should be such that the duration of contact between air and carbon is at least 1/3 second. The duration of contact is given by the formula:

$$\text{Duration of contact (sec.)} = 60 \times \frac{\text{Total volume of adsorbent bed (cm}^3\text{)}}{\text{gas flow rate (cm}^3\text{/min.)}}$$

To collect samples of low boiling vapors, for which activated carbon has a retentivity of 5 per cent or less (TABLE 3), a carbon bed of at least 1½ inch uniform thickness in the direction of air flow and a duration of contact between air and carbon of at least 2/3 second should be used. As noted previously, such sampling of low boiling vapors may not be quantitatively efficient unless the sorbent is refrigerated or chemically impregnated.

When the initial concentration of gas or vapor in the atmosphere to be sampled is very low and it is desired to concentrate the gas or vapor from large volumes of air, it is convenient to arrange the carbon bed in a cylindrical canister,[21] as shown in FIGURE 2. The use of a relatively thin bed makes it possible to draw or push large volumes of air through the carbon bed with the aid of an inexpensive blower (FIGURE 3).

When adsorption with chemical reaction (chemisorption) will facilitate analysis, the adsorbent is first impregnated with a suitable reagent. Thereafter the sampling procedure is the same as that described for physical adsorption. The method of desorption (see pages 208–209) will depend on the analytical requirements.

Typical impregnations for chemisorption include the following:

Odorant	*Impregnant for chemisorption on activated carbon*
Ammonia	Sulfuric acid
Arsine	Copper and silver oxidation catalysts
Ethylene	Bromine
Formaldehyde	Stabilized sodium sulfite
Hydrogen sulfide	Lead acetate or silver cyanide

Silica gel may advantageously be used for short-duration sampling from atmospheres which contain sufficiently high concentrations of odorant gases or vapors or which are sufficiently dry so that the adsorbent does not become moisture-saturated before the sampling is complete.[4,6,17] Although

Table 3

Retentivity* of Vapors by Activated Carbon
(% Retained in a Dry Air Stream at 20° C 760 mm. by Weight)

Substance	*Formula*	*Molecular Weight*	*Normal Boiling Point°C. 760 mm.*	*Approx. Retentivity in % at 20° C. 760 mm.*	*Characteristics*
Acetaldehyde	C_2H_4O	44.1	21	7	Reagent; apple stimulant
Acetic acid	$C_2H_4O_2$	60.1	118	30	Reagent; sour vinegar
Acetone	C_3H_6O	58.1	56	15	Solvent
Acetylene	C_2H_2	26.0	−88	2	Welding and cutting
Acrylaldehyde	C_3H_4O	56.1	52	15	Acrolein, burning fats
Acrylic acid	$C_3H_4O_2$	72.1	142	20	Plastic monomer
Ammonia	NH_3	17.0	−33	Negligible	Refrigerant
Amyl acetate	$C_7H_{14}O_2$	130.2	148	34	Lacquer solvent
Amyl alcohol	$C_5H_{12}O$	88.1	138	35	Fusel oil
Benzene	C_6H_6	78.1	80	24	Benzol, paint solvent and remover
Body odors	—	—	—	High	
Bromine	Br_2	159.8	59	40 (dry)	Organic synthesis
Butane	C_4H_{10}	58.1	1	8	Fuel
Butyl acetate	$C_6H_{12}O_2$	116.2	126	28	Lacquer solvent
Butyl alcohol	$C_4H_{10}O$	74.1	118	30	Solvent
Butyl chloride	C_4H_9Cl	92.6	78	25	Solvent
Butyl ether	$C_8H_{18}O$	130.2	142	20	Solvent
Butylene	C_4H_8	56.1	−5	8	Fuel
Butyne	C_4H_6	54.1	27	8	Organic synthesis
Butyraldehyde	C_4H_8O	72.1	76	21	Present in internal combustion exhaust
Butyric acid	$C_4H_8O_2$	88.1	164	35	Sweat, body odor
Camphor	$C_{10}H_{16}O$	152.2	204	20	Medicinal; preservative
Caprylic acid	$C_8H_{16}O_2$	144.2	238	35	Animal odor
Carbon bisulphide	CS_2	76.1	46	15	Solvent
Carbon tetrachloride	CCl_4	153.8	76	45	Solvent; cleaning fluid; fire extinguisher
Chlorine	Cl_2	70.9	−34	15 (dry)	
Chloroform	$CHCl_3$	119.4	61	40	Solvent; anesthetic
Cooking odors	—	—	—	High	
Cresol	C_7H_8O	108.1	202	30	Wood preservative
Crotonaldehyde	C_4H_6O	70.1	104	30	Solvent; tear gas
Decane	$C_{10}H_{22}$	142.3	231	25	Ingredient of kerosene
Diethyl ketone	$C_5H_{10}O$	86.1	103	30	Solvent
Ethyl acetate	$C_4H_8O_2$	88.1	77	19	Lacquer solvent
Ethyl alcohol	C_2H_6O	46.1	78	21	Grain alcohol
Ethyl chloride	C_2H_5Cl	64.5	12	12	Refrigerant; anesthetic
Ethylene	C_2H_4	28.0	−104	3	More retentivity by bromination. Illuminating gas; fruit ripener
Ethyl ether	$C_4H_{10}O$	74.1	35	15	Medical ether
Ethyl mercaptan	C_2H_6S	62.1	35	23	Garlic; onion; sewer
Essential oils	—	—	—	High	
Eucalyptole	$C_{10}H_{18}O$	154.2	176	20	

TABLE 3—*Continued*

RETENTIVITY* OF VAPORS BY ACTIVATED CARBON

Substance	*Formula*	*Molecular Weight*	*Normal Boiling Point°C. 760 mm.*	*Approx. Retentivity in % at 20° C. 760 mm.*	*Characteristics*
Food (raw) odors	—	—	—	High	
Formaldehyde	CH_2O	30.0	−21	3	More retentivity by impregnation. Disinfectant; plastic ingredient
Formic acid	CH_2O_2	46.0	101	7	Reagent
Heptane	C_7H_{16}	100.2	98	23	Ingredient of gasoline
Hexane	C_6H_{14}	86.2	69	16	Ingredient of gasoline
Hexyne	C_6H_{10}	82.1	71	16	
Hydrogen bromide	HBr	80.9	−67	8	Strong acid
Hydrogen chloride	HCl	36.5	−84	4	Strong acid
Hydrogen fluoride	HF	20.0	19	8	Strong acid
Hydrogen iodide	HI	127.9	−35.4 (4 atm)	15	Strong acid
Hydrogen sulphide	H_2S	34.1	−62	3 (dry)	Oxidizes to increase retentivity considerably
Indole	C_8H_7N	117.1	254	25	Excreta
Iodine	I_2	253.8	183	40	Antiseptic
Iodoform	CHI_3	393.8	Sublimes	30	Antiseptic
Isopropyl acetate	$C_5H_{10}O_2$	102.1	89	23	Lacquer solvent
Isopropyl alcohol	C_3H_8O	60.1	82	26	Solvent; antifreeze
Isopropyl chloride	C_3H_7Cl	78.5	35	20	Solvent
Isopropyl ether	$C_6H_{14}O$	102.2	68	18	Solvent
Lactic acid	$C_3H_6O_3$	90.1	122	30	Sour milk
Menthol	$C_{10}H_{20}O$	156.3	215	20	Medicinal
Methyl acetate	$C_3H_6O_2$	74.1	57	16	Solvent
Methyl alcohol	CH_4O	32.0	65	10	Wood alcohol
Methyl chloride	CH_3Cl	50.5	−24	5	Refrigerant
Methylene chloride	CH_2Cl_2	84.9	40	30	Organic synthesis
Methyl ether	C_2H_6O	46.1	−24	10	
Methyl ethyl ketone	C_4H_8O	72.1	80	25	Solvent
Methyl isobutyl ketone	$C_6H_{12}O$	100.2	116	30	Solvent
Methyl mercaptan	CH_4S	48.1	8	20	Skunk, sewer, etc.
Naphthalene	$C_{10}H_8$	128.2	218	30	Reagent; moth balls
Nicotine	$C_{10}H_{14}N_2$	162.2	247	25	Tobacco
Nitric acid	HNO_3	63.0	86	20	Oxidizing acid
Nitrobenzene	$C_6H_5NO_2$	123.1	211	20	Oil of bitter almonds; oil of mirbane
Nitrogen dioxide	NO_2	46.0	21	10	Hydrolyzes to increase retentivity
Nonane	C_9H_{20}	128.2	150	25	Ingredient of kerosene
Octane	C_8H_{18}	114.2	125	25	Ingredient of gasoline
Ozone	O_3	48.0	−112	Decomposes to oxygen	Generated by electrical discharge

Table 3—*Concluded*
Retentivity* of Vapors by Activated Carbon

Substance	*Formula*	*Molecular Weight*	*Normal Boiling Point°C. 760 mm.*	*Approx. Retentivity in % at 20° C. 760 mm.*	*Characteristics*
Packing house odors. .	—	—	—	High	
Palmitic acid.	$C_{16}H_{32}O_2$	256.4	339	35	Palm oil
Pentane.	C_5H_{12}	72.1	37	12	Light naphtha
Pentylene.	C_5H_{10}	70.1	40	12	
Phenol.	C_6H_6O	94.1	182	30	Carbolic acid; plastic ingredient
Propane.	C_3H_8	44.1	−42	5	Heating gas
Propionic acid.	$C_3H_6O_2$	74.1	141	30	
Propylene.	C_3H_6	42.1	−47	5	Coal gas
Propyl mercaptan. . . .	C_3H_8S	76.1	68	25	Skunk
Propyne.	C_3H_4	40.1	−23	5	Organic synthesis
Putrescine.	$C_4H_{12}N_2$	88.2	158	25	Decaying flesh
Pyridine.	C_5H_5N	79.1	115	25	Burning tobacco
Sewer odors.	—	—	—	High	
Skatole.	C_9H_9N	131.2	266	25	Excreta
Sulfur dioxide	SO_2	64.1	−10	10 (dry)	Oxidizes to sulfur trioxide; common in city atmospheres
Sulfur trioxide. . . .	SO_3	80.1	45	15 (dry)	Hydrolyzes to sulfuric acid
Sulfuric acid.	H_2SO_4	98.1	330	30	
Toilet odors.	—	—	—	High	
Toluene.	C_7H_8	92.1	111	29	Manufacture of TNT
Turpentine.	$C_{10}H_{16}$	136	180	32	Solvent
Valeric acid.	$C_5H_{10}O_2$	102.1	187	35	Sweat; body odor; cheese
Water.	H_2O	18.0	100	None	
Xylene.	C_8H_{10}	106.2	144	34	Solvent

* The Retentivities indicated apply to activated carbon of specifications of Table 2.

silica gel has a lower capacity and retentivity for organic odorants than does activated carbon, it exhibits a greater selectivity among them. Therefore, (a) desorption of odorants from silica gel is easier than from activated carbon (see pages 208–209), (b) it is feasible to obtain some separation of odorants by selective desorption from silica gel, and (c) the use of silica gel should be restricted to sampling the heavier odorous vapors (liquid at ordinary temperatures) or those for which it exhibits a chemical affinity. The light background afforded by silica gel or activated alumina can also be used to advantage in chemisorption by permitting the direct observation of chemical changes on the adsorbent surface. Thus, for example, silver cyanide on activated alumina is used to detect hydrogen sulfide.

Collection by Absorption. Equipment for absorption may consist of a

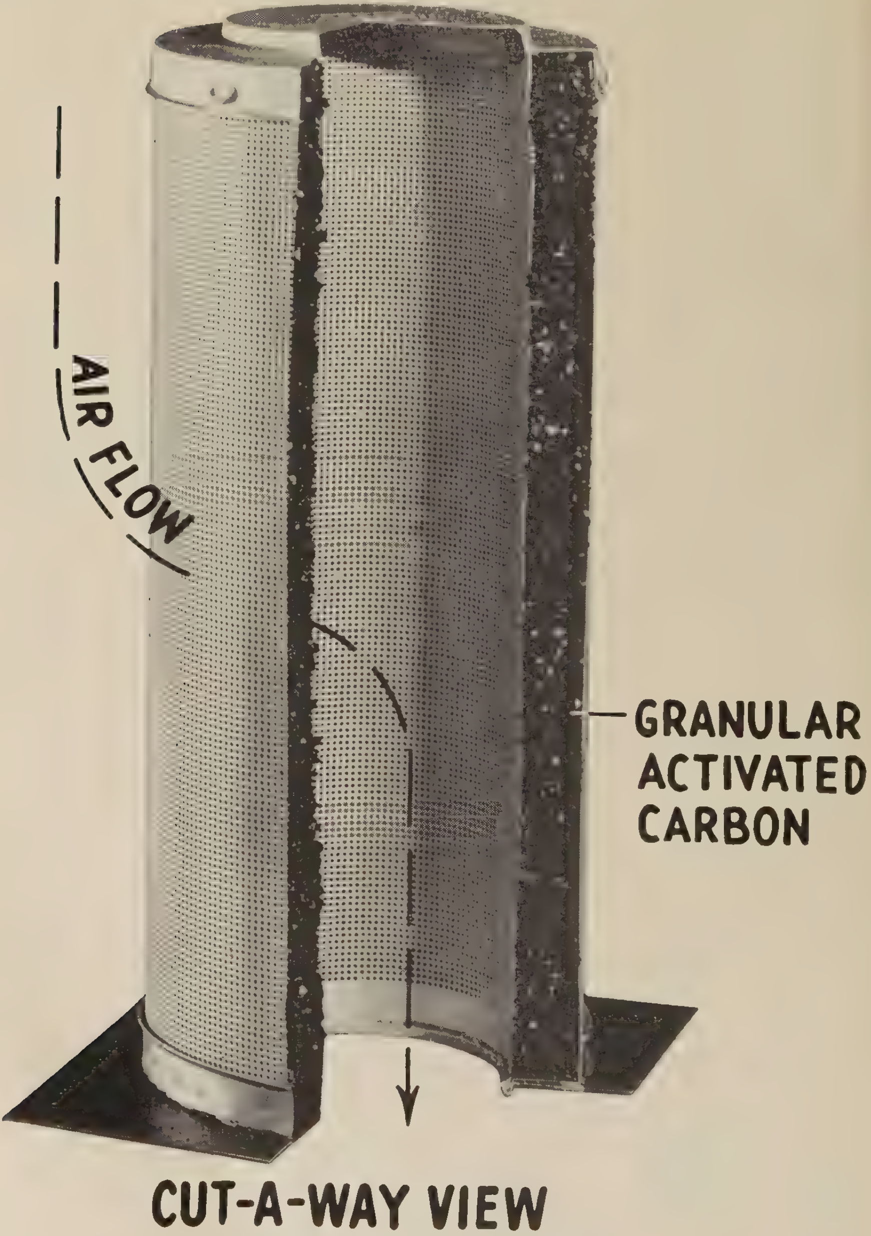

FIGURE 2. Activated carbon canister.

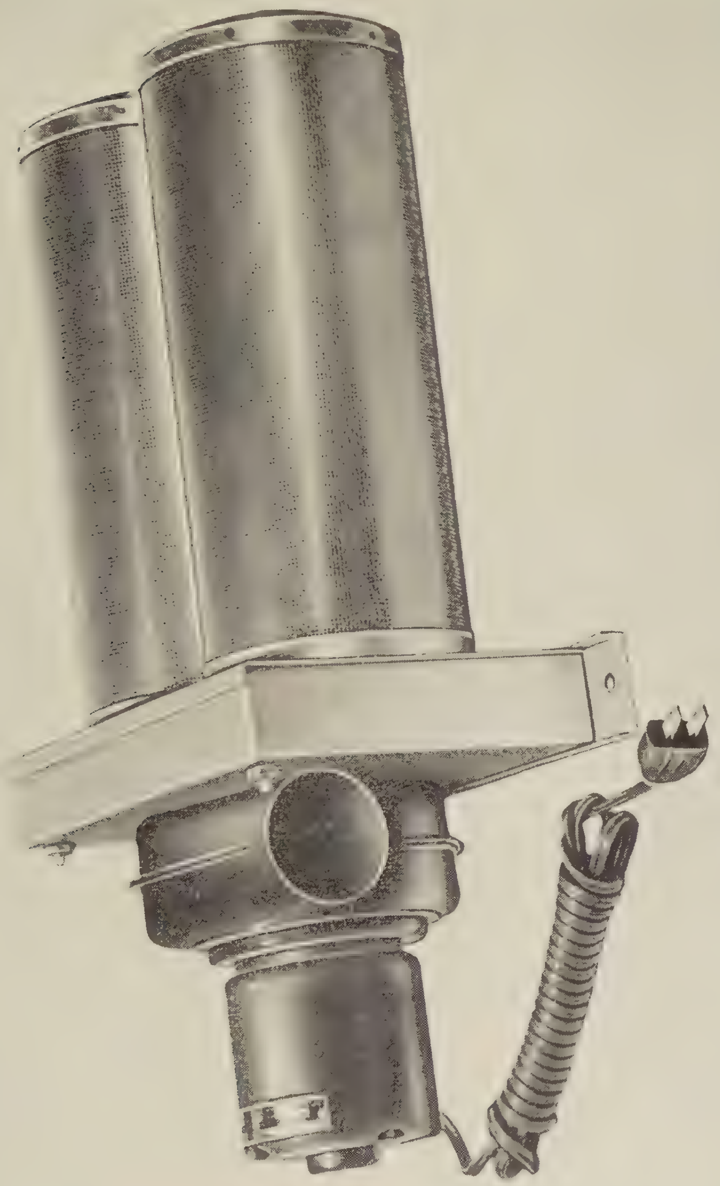

FIGURE 3. Activated carbon collector unit.

simple bubbler, a liquid impinger, a bubbler in which the air is broken into many small streams before entering the liquid phase, a bubbler in which the gas is forced through a long or tortuous path through the solvent, or a spray chamber.[1, 20] The bubbler in which the gas stream is finely divided (usually by a sintered glass disc) is generally the most satisfactory device, gas-liquid contact efficiencies being reliably over 90 per cent through wide ranges of flow. This and other absorption equipment with high gas-liquid contact efficiencies usually suffer by having relatively low flow capacities.

For absorption of odorants from air without chemical reaction by scrubbing the air with a solvent, the following factors must be considered: (a) aqueous solvents are not suitable for many organic odorants, hence some organic solvent or mixture is needed; (b) during the prolonged sampling often necessary to collect measurable quantities of odorants, repeated replacement of evaporated solvent may be necessary; (c) when organic odorants have been collected as a very dilute solution in an organic solvent, the problem of their recovery is formidable. In fact, it will often be very difficult to distinguish the dissolved odorants from the impurities present in the initial solvent. The use of modern double-beam infrared spectrum recording equipment, however, makes it possible to record directly the difference between the infrared spectrum of the initial solvent and of the solvent which has been used for atmospheric sampling. This difference between the two spectra may be taken as the spectrum of the collected odorous impurities. This method gives only a measure of the general organic functionalities of the odorants in the sampled air, and does not directly assist in separating the odorants into their individual components.

Several methods of absorbing odors with chemical reaction have been reported.[3, 7, 10, 11, 12, 13] The general limitation of all of these methods lies in the fact that there is no workable relation between odor and chemical reactivity. The reactions most commonly used for absorbing odorants have been oxidation, usually by permanganate or ceric oxidants. Chemical methods fail to solve the problem of isolation of the individual components of odorous air when the action is irreversible. Some exceptions, where the odorant can be regenerated, include hydrogen sulfide (absorbed by aqueous lead acetate, regenerated by acid), ammonia (sulfuric acid; sodium hydroxide), aldehydes (sulfurous acid; sodium carbonate), and olefins (acid mercuric perchlorate; hydrochloric acid).

Collection by Condensation. Collection of odorants by condensation at low temperatures has a number of distinct advantages over any other collection method. First, the collected odorous material is immediately available for further separation or analysis, without requiring the removal of solvents or desorption from an adsorbent. Second, condensation is the most reliable method for preserving the odorants without chemical reaction with any part of the collecting device or among themselves. The main disadvantages of collection by condensation are that the equipment is cumbersome and requires rather frequent attention and that large quantities of water are always condensed together with the collected odorants. However, the admixture of atmospheric odorants with water is not too serious a problem because their extraction from it is experimentally simple.

A special problem in low temperature collection technique is caused by the formation of condensation mists when the sampled air is cooled. Such mists are composed of solid or liquid particles of widely varying sizes, and often pass through the cold traps in sufficient proportion to reduce significantly the collection efficiency of the equipment. It is, therefore, necessary to provide a simple filter, such as a glass wool plug, within the cold trap to minimize such losses of particulate matter produced by condensation. As collection proceeds, the solid condensate which forms in the trap acts as a filter and collection efficiency becomes higher and higher until the resistance of the equipment to air flow becomes prohibitive. Several interesting studies of collection efficiencies by condensation have been reported.[2, 9, 16]

In selecting refrigerants for vapor concentration, it is most common to use materials which maintain a constant temperature by change of phase. A representative group of such refrigerants available for low temperatures is given in TABLE 4. Liquid oxygen is generally the coldest permissible refrigerant for the collection of atmospheric odorants, because any lower trap temperatures (*e.g.*, liquid nitrogen refrigerant) may condense atmospheric oxygen in the trap, especially at low sampling rates. The important fire hazard of liquid oxygen must be recognized.

TABLE 4
REFRIGERANT TEMPERATURES

Refrigerant System	*Temperature, °C.*
O_2 (l) $\leftrightarrows$ O_2 (g)	−183.0
CS_2 (s) $\leftrightarrows$ CS_2 (l)	−118.5
CO_2 (s) $\leftrightarrows$ CO_2 (g)	−78.5
NH_3 (l) $\leftrightarrows$ NH_3 (g)	−33.4
H_2O (s) $\leftrightarrows$ H_2O (l)	0

TABLE 1 adapted from Sanderson,[18] presents vapor pressure data for the lightest odorants of each of the important organic homologous series and of some inorganic odorants at the temperature of commonly available cooling baths. Some of these data are shown graphically in FIGURE 1. For condensing a given odorant, it is necessary to select a refrigerant sufficiently cold for the vapor pressure of any trapped odorant to be low enough to prevent significant evaporation during the sampling. Generally, the vapor pressure of condensed odorants should be about 1 mm. or lower at trap temperatures. The method most frequently used employs a series of traps at progressively lower temperatures, thus affording some degree of fractional condensation and, if the last trap is empty, some assurance of efficient condensation.

A typical condensation trap, as reported by Shepherd,[19] is the sampling tube S in FIGURE 4. The fractionation procedure used with this sampler is elaborated in an ensuing discussion of mass spectral analysis.

Techniques of collection by low-temperature condensation and adsorption may be effectively combined, as by the use of activated carbon or silica gel at liquid air temperature. Such methods, though promising, have not been used extensively.

Analysis

Quantitative Analysis. The purpose of quantitative analysis of odorous gases and vapors is to give only a conglomerate measure of the quantity of odorants in a given volume of air, without regard to their qualitative composition or odorous quality or intensity. Such quantitative analysis has been carried out mainly by two methods: (a) oxidimetry and (b) quantitative measure of carbon adsorption.

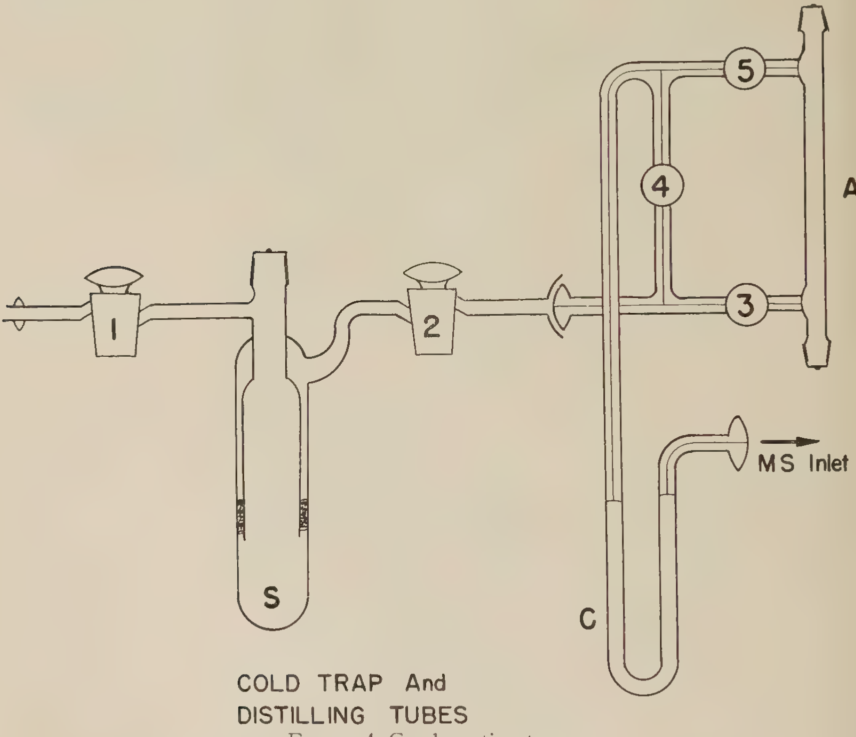

FIGURE 4. Condensation trap.

Oxidimetric methods (employing permanganates or ceric salts), as stated previously, do not give information of particular value in the study of odorants because of the lack of relationship between quality or intensity of odorants and their reactivity toward a chemical oxidant. A method of measuring atmospheric oxidants continuously by a reducing method has also recently been reported.[23] Results achieved by such methods determine only the reducing or oxidizing qualities of the extraneous atmospheric gases and vapors and further interpretations therefrom are not generally valid.

The method of quantitative analysis by carbon adsorption, on the other hand, permits the calculation of results in terms of weights of odorants per unit volume of air. This is valuable because it provides information which is useful when methods of control of atmospheric odor are to be considered. Further, the sorbed odorants are available for qualitative analysis by desorbing them from the carbon, in contrast to the method of oxidation, which chemically destroys the odorants.

Quantitative Analysis of Odorous Gases and Vapors by the Carbon Sorption Method: Units. Concentration of odorous vapors shall be expressed in units of mg. of odorous vapors per 1000 l. of air. If the average molecular weight of the odorous vapors is known or assumed, then the concentration of odorous vapors in parts per million by volume, referred to 0°C. and one atmosphere pressure, is:

$$C_v = \frac{22.4C_w}{M}$$

where C_v = concentration of odorous vapors by volume (ppm.).
C_w = concentration of odorous vapors by weight (mg. per 1000 l.)
M = average molecular weight of odorous vapors.

Measurement of Concentration of Odorous Vapors. At least 50 g. of activated carbon, which satisfies the specifications shown in TABLE 2, previously dried for six hours at 150°C. and weighed, are used to collect atmospheric odorous vapors by the sampling method previously described (see section, "Collection by Adsorption", pages 201 and 204). The duration of the sampling period should be such that approximately 1000 to 5000 l. of air (depending on its degree of contamination) per g. of carbon are passed through the carbon bed. After the sampling, the adsorbent is weighed and the value recorded. The moisture content of the entire sample (if it weighs 100 g. or less), or of a representative 50 to 100 g. portion, is then determined by a xylene distillation method. The carbon sample is completely covered with dry xylene in a 500 ml. flask fitted with a Stark and Dean moisture trap and a reflux condenser. The mixture is allowed to distill for ½ hour, at which time the amount of water in the trap is read and recorded.

If it is known or suspected that some of the odorous vapors are water-soluble, it will be necessary to withdraw an aliquot sample of the aqueous layer from the Stark and Dean moisture trap and determine the proportion of water in the aliquot by a chemical aquametric method such as the Karl Fischer titration. The amount of water in the total carbon sample is then calculated as follows and recorded:

$$\begin{array}{l}\text{Total water}\\ \text{adsorbed (g.)}\end{array} = \begin{array}{l}\text{Wt. of aqueous}\\ \text{layer obtained}\\ \text{in trap (g.)}\end{array} \times \begin{array}{l}\text{Proportion of}\\ \text{water in}\\ \text{aqueous layer}\end{array} \times \frac{\begin{array}{l}\text{Wt. of total carbon}\\ \text{sample (g.)}\end{array}}{\begin{array}{l}\text{Wt. of carbon sample}\\ \text{used for moisture}\\ \text{det'n. (g.)}\end{array}}$$

Then the degree of saturation of the carbon with nonaqueous material is calculated by:

$$\text{Degree of nonaqueous sat'n of carbon} = \frac{\text{Weight of carbon after sampling} - \text{Weight of carbon before sampling} - \text{Weight of total water absorbed}}{\text{Weight of carbon before sampling}}$$

This degree of saturation of the carbon should fall between approximately 0.02 and 0.12, otherwise the sampling should be repeated with an appropriate adjustment in the ratio of volume of sampled air per unit weight of carbon. Then the concentration of odorous vapors in the sampled air is given by:

$$\underset{\text{(mg. per 1000 l.)}}{C_w} = \frac{1.67\ (10)^4 \times \text{Degree of nonaqueous sat'n of carbon (g.)} \times \text{Wt. of carbon before sampling}}{\text{Rate of air flow during sampling (l./min.)} \times \text{Duration of sampling (hr).}}$$

The constant in the equation is dimensional only—to permit the use of the most convenient units for each term.

To avoid loss of time in adjusting the ratio of volume of sampled air to unit weight of carbon, it is advantageous to start the determination with two or more replications of the sampling equipment. Then the first analysis for degree of saturation of the carbon can conveniently be carried out after a relatively short sampling period. If this analysis shows that the degree of saturation of the carbon is below 0.02 and the duration of the sampling was thus insufficient, the duplicate sampling equipment can be allowed to operate for a proportionately longer time calculated to saturate the carbon within the range of 0.02 to 0.12. In this way, no time need be lost in repetitions of the sampling.

Qualitative Analysis of Odorous Gases and Vapors. Odorous gases and vapors can be isolated for qualitative analysis from material collected either by the carbon sorption or the condensation methods. When the carbon sorption method is used, it is necessary to start with a sample sufficiently large for carbon to be available both for moisture determination and desorption.

There are two methods of desorption: (a) displacement of the adsorbed organic vapors by a hot inert vapor such as steam, and (b) heating the carbon under vacuum and distilling the desorbed material into cold traps.

For steam displacement, the saturated carbon is flushed with superheated steam at 300°C. or higher. The effluent steam and displaced vapors are condensed and held for analysis. Flushing is continued until the condensate is substantially odorless. Upon standing, the condensate may separate into an oily and an aqueous layer. Both oily and aqueous fractions may then be subjected to qualitative chemical or spectrometric analysis for detection of inorganic ions and organic functional groups. The steam displacement method, although very effective as a means of desorption, suffers from the disadvantage that steam will hydrolize some organic compounds, such as esters, thereby causing qualitative changes. This effect can be circumvented by using the vacuum method described in the following paragraph.

For vacuum desorption, the saturated carbon is connected to a train of three traps in series (FIGURE 5), which are immersed in ice-salt, dry ice-cellosolve and liquid nitrogen, respectively. Stopcocks C and E are closed and the entire system is evacuated with the mechanical forepump only. After one-half hour the diffusion pump is started and pumping is continued for three hours at a pressure of about one micron. During the pumping, the carbon sample is held at a temperature of 200–250°C. At the end of the pumping period, the system is slowly returned to atmospheric pressure by bleeding in air or nitrogen through stopcock C. (Caution: In following this procedure, care must be exercised to avoid condensing atmospheric oxygen in the liquid nitrogen trap. If necessary, the trap should be warmed up to dry ice temperature before bleeding in air.) The traps are then removed and their contents examined. Most of the water and some nonaqueous matter will be found in the ice-salt trap, most of the odorous organic material and some water in the dry ice trap, and some of the lighter odorous material in the liquid nitrogen trap. These materials, with or without further fractionation, may be subjected to chemical or spectrometric qualitative analysis.

As an alternative procedure, the system may first be evacuated with a water aspirator pump only (stopcock C), with the carbon held at 100° C. This strips the carbon of most of its moisture and little else. The first trap may then be emptied and pumping resumed at lower pressures as described in the preceding paragraph.

For desorbing odorous gases or vapors from silica gel, less drastic methods are adequate. The use of superheated steam or high vacuum is unnecessary. Blowing with contaminant-free air at temperatures up to 350° has been found to be effective in removing gases and vapors sorbed on silica gel.

Qualitative Spectral Analysis. Infrared spectra are particularly valuable for characterizing individual odorants or for revealing the chemical nature of a mixture of odorants. The use of infrared spectra for qualitative examination of organic compounds depends on the fact that atoms of organic molecules vibrate with definite characteristic frequencies, causing the compound to exhibit selective absorption in the infrared region of the spectrum. In establishing the spectrum, infrared light of all wavelengths is passed through a thin layer of the material being tested. Those wavelengths which correspond to the vibrational frequencies of the molecules are absorbed while others are transmitted. Different functional groups, such as aldehyde, alcohol, and ester linkages, show typical infrared absorption frequencies. Thus the infrared spectrum of a mixture of compounds reveals information on the types of individual compounds therein.

In special cases, interpretation of infrared spectra or mixtures can yield very significant results. For example, in comparing the infrared spectra of

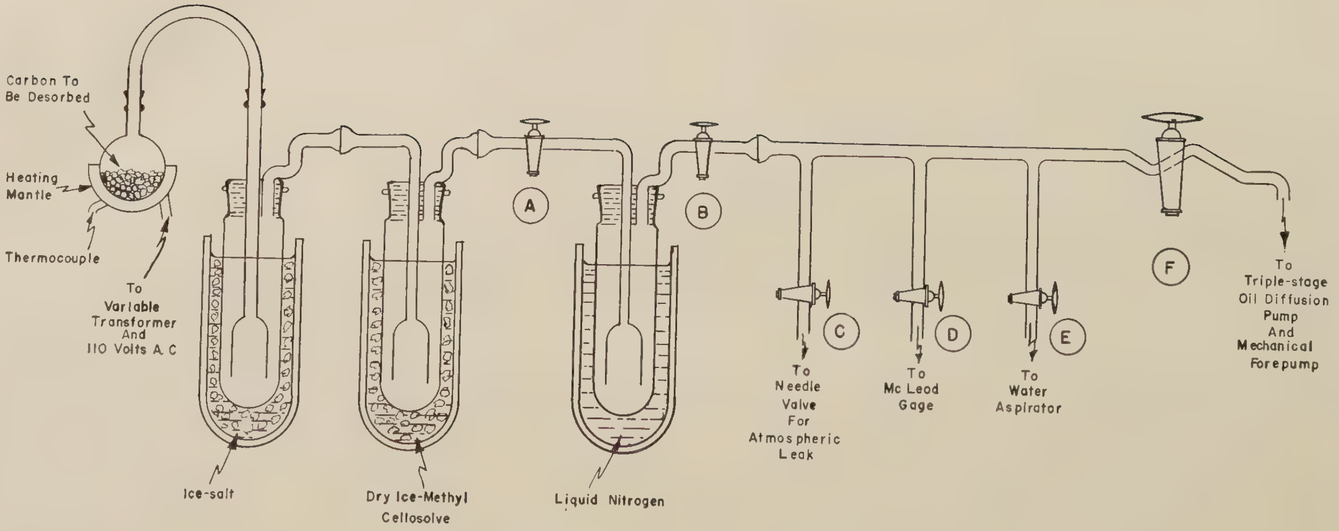
Carbon To Be Desorbed
Heating Mantle
Thermocouple
To Variable Transformer And 110 Volts A C
Ice-salt
Dry Ice-Methyl Cellosolve
Liquid Nitrogen
A
B
C
D
E
F
To Needle Valve For Atmospheric Leak
To Mc Leod Gage
To Water Aspirator
To Triple-stage Oil Diffusion Pump And Mechanical Forepump

FIGURE 5. Apparatus for vacuum desorption of carbon.

vapors emanating from (a) common green lemon mold and (b) one of its mutants produced by irradiation,[25] it was apparent that the major significant difference was the absence of any chemical unsaturation in the mixture from the mutated mold (FIGURE 6). Thus the infrared spectra of two mixtures of vapors, uniquely demonstrated the important difference between them without the necessity of separating such vapors into their individual components. In another example, by combining partial chemical isolation with measurement of infrared spectra, it was demonstrated that one of the vaporous components of apple aroma present in a commercial apple storage room was the mineral oil vaporized from impregnated fruit wrapping material.[26] Infrared spectra have also been used to determine the chemical functionalities of odorants in various areas in the City of Philadelphia.[16]

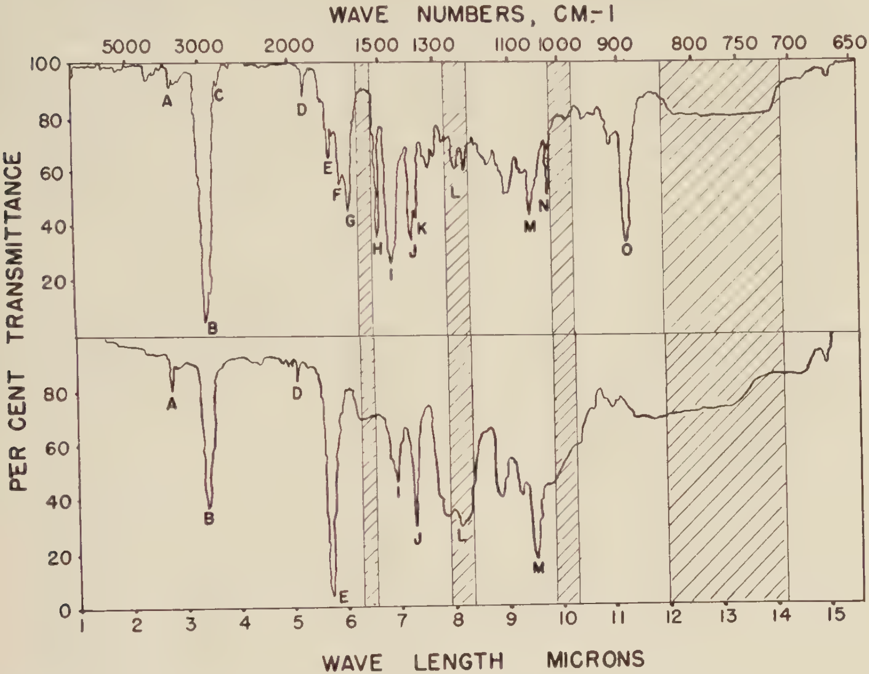

FIGURE 6. Infrared spectra of vapors from green lemon mold.

Qualitative Analysis by Mass Spectra. The mass spectrograph, first built before 1920 by Aston and by Dempster, is an instrument which separates atomic and molecular particles according to their masses. Its most important early use was in the separation of isotopes, atoms of the same element which differ in mass. Only within the last few years has this method been used to make precise analyses of more complex gas mixtures. Work along these lines was first directed mostly to mixtures of petroleum gases.

When a single compound gas is subjected to mass spectral analysis, the result obtained shows not only its molecular mass but also the masses of the fragments split off in the ionization process. This spectrum, or "cracking pattern," is unique for each substance. When a complex mixture of gases is subjected to such analysis, the resulting composite spectrum must be mathematically analyzed to define the individual mass spectral cracking patterns of which it is composed. This assumes some information about the nature of the gases present and a previous knowledge of the cracking patterns of these likely components. This requires that much previous work must have been done with the types of mixtures to be investigated before the full benefit of this technique is realized. Such work has already been carried out by the petroleum industry for hydrocarbon gases, and mass spectral analysis is, therefore, extensively used in this field. In the case of odorous gases, the information thus far available includes the cracking patterns of some alcohols, esters, aldehydes, and other oxygenated compounds.[8, 14, 24] More specific and extensive background research is needed.

Since the interpretation of the mass spectrum of an odorous mixture depends on the knowledge of the individual spectra of the components, it will be greatly facilitated by any previous physical fractionation of the odorant mixture. Shepherd and his co-workers,[19] in analyzing the components of Los Angeles air, used a method of physical separation followed by mass spectral analysis to great advantage.

For further separation of trapped components prior to analysis, the sampler S (FIGURE 4) is used as a flask for isothermal distillation at progressively higher temperature levels. The material distilled at a given temperature is passed through drying tube A, which contains sufficient Ascarite to remove 300 ml. of atmospheric carbon dioxide, and thence into condenser C which is immersed in liquid nitrogen (stopcocks 2, 3, and 5 open). After distillation at a given temperature is complete, the fraction in condenser C is evaporated directly into the inlet system of a mass spectrometer, the calibrated volume of whose gasometric unit includes the space in C and the connections back to closed stopcocks 4 and 5. Some experimental difficulties inherent in this procedure include the adsorption of acidic or unsaturated organic vapors by the Ascarite and the collection of some water in condenser C. Typical compounds identified by Shepherd with the aid of this technique included acetylene, butanes, benzene, toluene, carbon tetrachloride, trichloroethylene, nitrous oxide, and sulfur dioxide. It was also possible to rule out many compounds as absent, and to list others as "probably present."

An alternative method of fractionation prior to mass spectral analysis used by the author[25] consists in subjecting progressively less volatile fractions to mass spectral analysis by allowing the contents of the condensation trap to evaporate directly into the spectrometer inlet. After each analysis, the trap contents are cooled in a constant temperature refrigerant, and all the matter which is volatile at the trap temperature is removed by evacuation. Progressively warmer refrigerants are used after each analysis, making less volatile components available to the spectrometer. This procedure serves to eliminate the spectral components of carbon dioxide fairly well without the use of any solid absorbent, but elimination is not so complete as can be obtained with Ascarite. Both methods have advantages, and the entire subject could benefit from further study. The use of both mass and infrared spectra to facilitate interpretation of the analysis of a mixture of odorants is complementary and hence valuable. Specific odorants cited as "probably present" in the odorous emanation from common green lemon mold included acetaldehyde, n- and isopropyl alcohols, methylacetate and ethyl formate.

The ultimate analysis of a mixture of atmospheric odorants will require painstaking and efficient methods of collection, judicious application of separation techniques by chemical crystallization, distillation or chromatographic methods, and the interpretation of mass and infrared spectral analyses of the separated components.

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STUDY AND EVALUATION OF THE ODOR PROPERTIES OF SURFACES

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Introduction

The application of the flavor profile method to the study of odorants and surfaces under various test conditions in the laboratory is discussed. Particular emphasis is placed upon the test procedures developed for this study, certain of the panel techniques employed, and the method used for the rating of odor properties such as pickup, release, and retention in connection with selected metallic and nonmetallic surfaces.

The results indicate a wide range of performance with respect to these properties by the surfaces studied. Useful evidence is presented which appears to have far-reaching implications concerning a number of commonly encountered industrial odor problems and points the way to a better understanding of many of the most serious and undesirable odor situations.

In one form or another, odor transfer plays an important role in most commonly encountered odor situations. In industry this usually means the contamination of one product or material by another. Examples of this phenomenon in action are many; contamination of food products by their containers, and the contamination during storage of an exposed material by a highly odoriferous one in the same vicinity are often-encountered examples of odor transfer.

The system becomes more complex when intermediate steps are involved. Then it no longer becomes a simple transfer from one material to another. It can become a confusing system whereby a material once contaminated may itself act as an odor source and in turn contaminate other materials. Surfaces of all types provide us with excellent examples of such intermediate odor sources. The surfaces in shipping drums and boxcars become contaminated with the odor of one material and then can contaminate any material subsequently placed in them. Another example with which we are all familiar is the odor which a silver spoon takes on after being in contact with onion soup and the troubles that arise when this spoon is used again.

More subtle forms of this phenomenon are found when a material picks up odor from the atmosphere surrounding it and, in some cases, innocently becomes an odor source; upholstery and draperies in the home can exhibit this tendency because of excessive cooking or tobacco odors in the air. The problems which arise, and potentially can exist, from odor transfer are numerous and find their way into most manufacturing operations.

A logical approach to obtaining a practical solution would appear to be a better understanding of the role surfaces play as intermediate odor sources. In this respect let us ask, "What is known about these odor properties of surfaces such as metals, plastics, and fabrics?" Not much has been reported on this subject. Zwaardemaker did some exploratory work early in the century on the adsorption powers of various materials for specific odorants.[1,2] But, by and large, the field is still open for more work.

Test Procedures

The odor chemists at Arthur D. Little, Inc. have been in close contact with the general problem for many years. During this period information has been gathered on hundreds of materials or combinations of materials. These studies have involved adaptations of a suitable method of odor measurement, the development of test procedures, and the analysis of data to provide a rating of odor properties. A broad field of exploration was covered, but the information given here should be considered preliminary.

Of the many materials studied, metals and coatings on metals have been selected for primary discussion at this time because they demonstrate a wide range of odor performance and have widespread usage. Tobacco smoke is the only odorant singled out for emphasis because it is a common odorant and offers a stringent test of a material's odor behavior.

Briefly, the procedure was as follows. Test strips of a number of materials were examined for initial odor by a trained odor group of four persons. The samples were then contaminated with tobacco smoke and examined for adsorbed odor. Next, they were submitted to a brief heating or purging period during which they were again examined by the odor panel. Materials were evaluated on the basis of the intensity and character of adsorbed odor and odor released during purging.

The contamination and purging procedure simulate at an accelerated rate the action that takes place on surfaces exposed in everyday atmospheres. Materials are constantly adsorbing and desorbing odors. Although release, or desorption, may be accelerated by high temperatures or an increase in temperature, some release will take place at room temperature.

The odor evaluation was done by a trained panel employing the flavor profile method [3] developed by Cairncross and Sjöström of Arthur D. Little, Inc. Only that portion of the method concerning odor was used. An adaptable method that has been used for studying a number of products, the profile method provides for a descriptive analysis of the sample under study, with intensities applied to the descriptive terms. An odor is usually complex, made up of a number of components. Some of these components, even though unidentifiable, contribute to the blend or background of the odor; certain of the components can be identified, and these give an odor its recognizable character.

To establish a profile of a material, the panel members individually study the sample and list the components using descriptive terms such as sour, rubbery, or burnt. Wherever possible, the names of specific chemicals are applied. The exact character of each odor note is discussed fully by the panel in an open session following the individual observation. A common terminology and understanding of each descriptive term is then adopted. The panel assigns an intensity to each individual odor component, using a scale ranging from "threshold," or "just perceptible," to "very strong."

A static system of odorization was selected because it would permit uniform exposure of the test surfaces. Experiments were made with tobacco smoke to establish the ideal test procedure. The method adopted produced satisfactory and reproducible pickup, yet minimized any opportunity for the odorant atmosphere to become stagnant or for odorant alteration to take place. A standard 10-inch laboratory vacuum desiccator was selected as the odorizing chamber, because it is easy to use and relatively easy to clean, even though glass is not immune to odor pickup. Since a strictly vapor-phase odorant was desirable, a trap consisting of an impingement tube containing a plug of nonabsorbent cotton was placed in the odorant introduction line to remove large smoke particles. A crimped pipe cleaner in the intake line at the juncture with the desiccator prevented any condensing tars from falling onto the test strips. With a desiccator, the number of test strips that could be contaminated by a single odorant introduction is limited, but the use of a number of such chambers allows for rapid screening of numerous samples. Four test strips of the same type were suspended from a glass rod in each desiccator. One hundred ml. of water were placed in the vessel to provide a humid atmosphere, and the chamber was evacuated to 15 mm. of mercury. Five cigarettes (each of a different brand) were placed in a manifold and smoked at a constant rate controlled by a water manometer held at the one-half-inch level. The cigarettes were removed when they had smoked down two inches. This produced a slow, steady smoking, not puffing, with the smoke being drawn through the impingement tube into the desiccator. The system was brought to atmospheric conditions for the exposure period, sealed, and allowed to stand for one hour. All tests were run at room temperature (70–80°F.). The apparatus, set up and ready for use, is shown in FIGURE 1.

The size of the test strips was determined by the need of sufficient area for odor examination. Strips were, in most instances, four by four inches. In so far as possible the thickness of the metal sample was 0.020 to 0.025 thousandths of an inch.

Whenever possible, metal strips were precleaned and baked at 250° F. for approximately four hours, before the first panel evaluation. After the odor had been introduced and the strips had remained in the sealed desiccator for one hour, the samples were removed and allowed to air for five minutes. The test strips were then examined to obtain a profile, with each panel member studying one strip. A typical panel session is shown in FIGURE 2. During the same panel session each member established a profile during a one-minute purging period over an infrared lamp.

Purging was accomplished by setting the strip 2 inches above a 250-watt infrared bulb encased in a section of galvanized tubing. The bulb was operated at 60 volts; the temperature of the test strips was in the region of 165° F. The strips were allowed to return to room temperature and at another panel session, several hours later, were examined for residual odor.

Although the method was used here under conditions of constant tem-

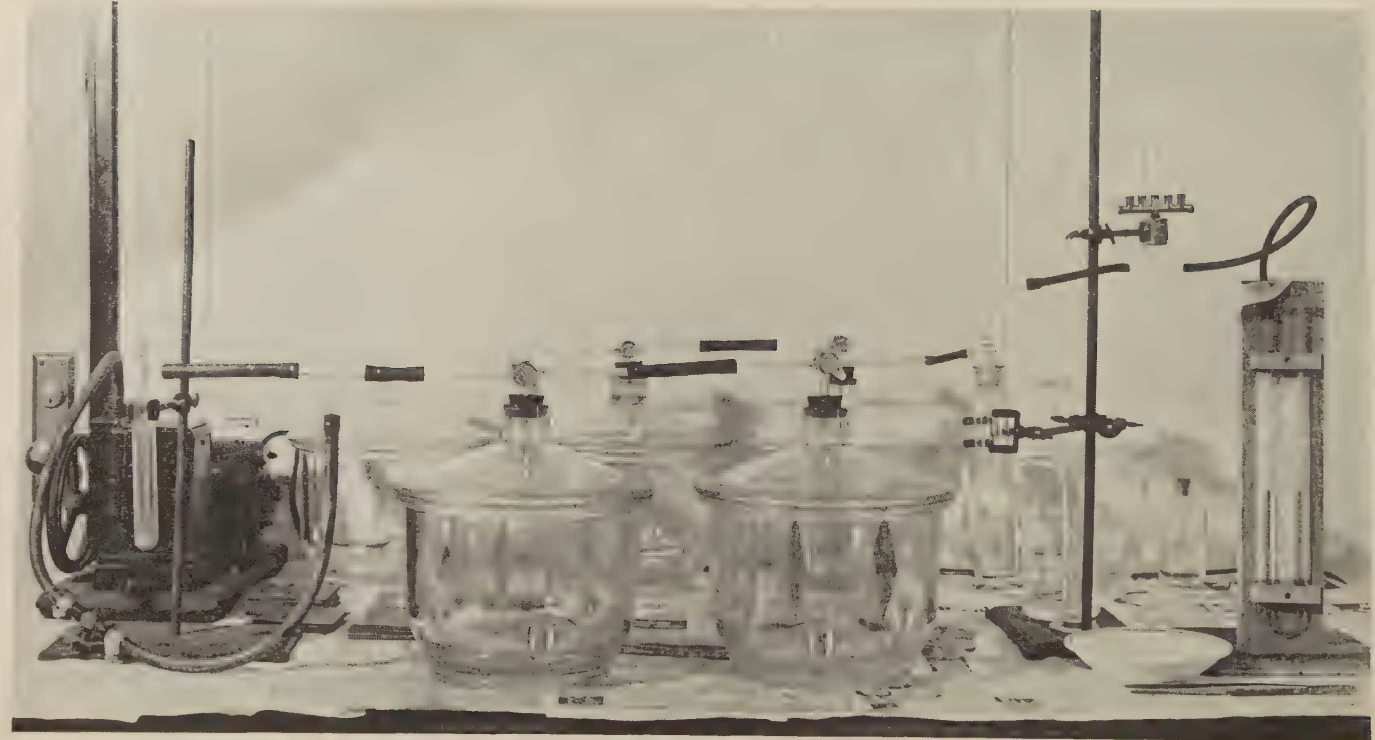


FIGURE 1.

perature and humidity, these factors may be varied for specific studies. The method may be used to study the effect of humidity, temperature, or odorants on the surface adsorption of odors.

Findings

The materials studied represented a wide range with respect to degree of odor pickup and the rate of release. In addition to this, another phenomenon, which may be an important key to many odor situations, was observed. It was noted that the great majority of the surfaces studied displayed an ability not only to pick up odor, but also to modify and distort it in the process. This distortion, in many instances, was so severe as to leave little suggestion of the original contaminant.

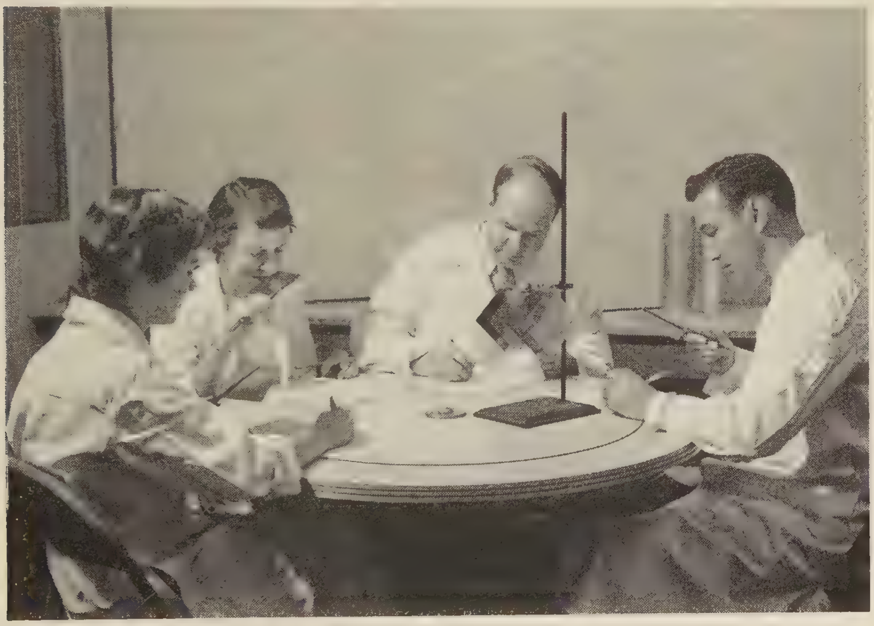


FIGURE 2.

This made it necessary, in evaluating samples, to do more than judge them according to the degree of pickup. Any realistic interpretation of the findings, therefore, must include evaluation of the odor character. Each such evaluation of odor type should fit the given odor situation. Useful information, however, can be gained by classifying, in a general way, the various odor components encountered. To accomplish this, each panel member, working independently, placed the descriptive terms into one of three arbitrary groupings, designated as "acceptable," "intermediate," or "objectionable." The rating was based upon the personal reaction to each odor component when it was encountered at an intensity level slightly in excess of recognition threshold. A change in intensity of a given note would, in all probability, mean a shift in its grouping. It was observed that an increase in intensity tended to make a note more objectionable.

Some of the components in the acceptable class included cementlike, dusty, metallic, and strawlike. Among those in the intermediate class were burnt (ironing board cover), fruity or estery, and sour.

The objectionable category included components which, by and large, were unexpected in tobacco smoke—odors which were accentuated by surfaces modifying the odorant. Among these objectionable components were stale cooking odors, footy, and various types of sulfide-bearing foods.

Each material was then rated on the basis of its odor pickup resistance. This was a term used to incorporate both the type and level of odor pickup. The rating scale was divided into four distinct categories: "good," "fair," "poor," and "very poor." For example, if the odor level was low, and the type of odor not objectionable, the surface received a "good" rating. Conversely, a surface exhibiting objectionable components at a high level merited a "very poor" rating.

The rate of release or the speed of purging the adsorbed odor was also considered to be of major importance. Those materials which rapidly returned to their original odor during the purging period and, therefore, had little or no residual odor were given a "rapid" rating; those which lost only a small part of the acquired odor during purging and retained a residual odor of high intensity were given "slow" ratings. TABLE 1 shows a plot of odor pickup resistance versus purging rate.

It may be interesting to consider how the odor properties of a metal can be changed. Various treatments of copper, and coatings on copper, demonstrate varied odor ratings. Electrolytic or commercial copper has poor pickup resistance to tobacco smoke and a slow purging rate. Anyone who has ever smelled a copper ashtray realizes this. Copper's low rating is due, in part, to its property of modifying the odor it adsorbs; specifically, for tobacco smoke, it adds such disagreeable odor components as stale cooking odors and decayed vegetables. Copper demonstrates that the purity of the metal does not affect the odor properties, for 99.9999 per cent pure copper has the same rating as commercial grade copper. Aluminum further indicates that purity does not affect the odor rating. It is reasoned that buffing a material might improve its odor rating, possibly through a reduction of available surface area. This appears to be the case with aluminum, although buffing does not appear to cause any appreciable improvement in copper. Conversely, it would be expected that an increase in surface area would cause a poorer pickup resistance. "Anodized" copper demonstrates that this is true.

For further analysis of this data, certain assumptions have to be made. If, for example, good pickup resistance and fast purging are considered the most desirable characteristics of a surface, TABLE 1 could be rearranged to show surfaces rated according to this assumption. TABLE 2 shows this. The best materials therefore are at the top of the diagram with a Good-Rapid rating; the second best are Good-Moderate and Fair-Rapid; and so

TABLE 1
ODOR RATINGS OF METALS AND COATINGS ON METALS

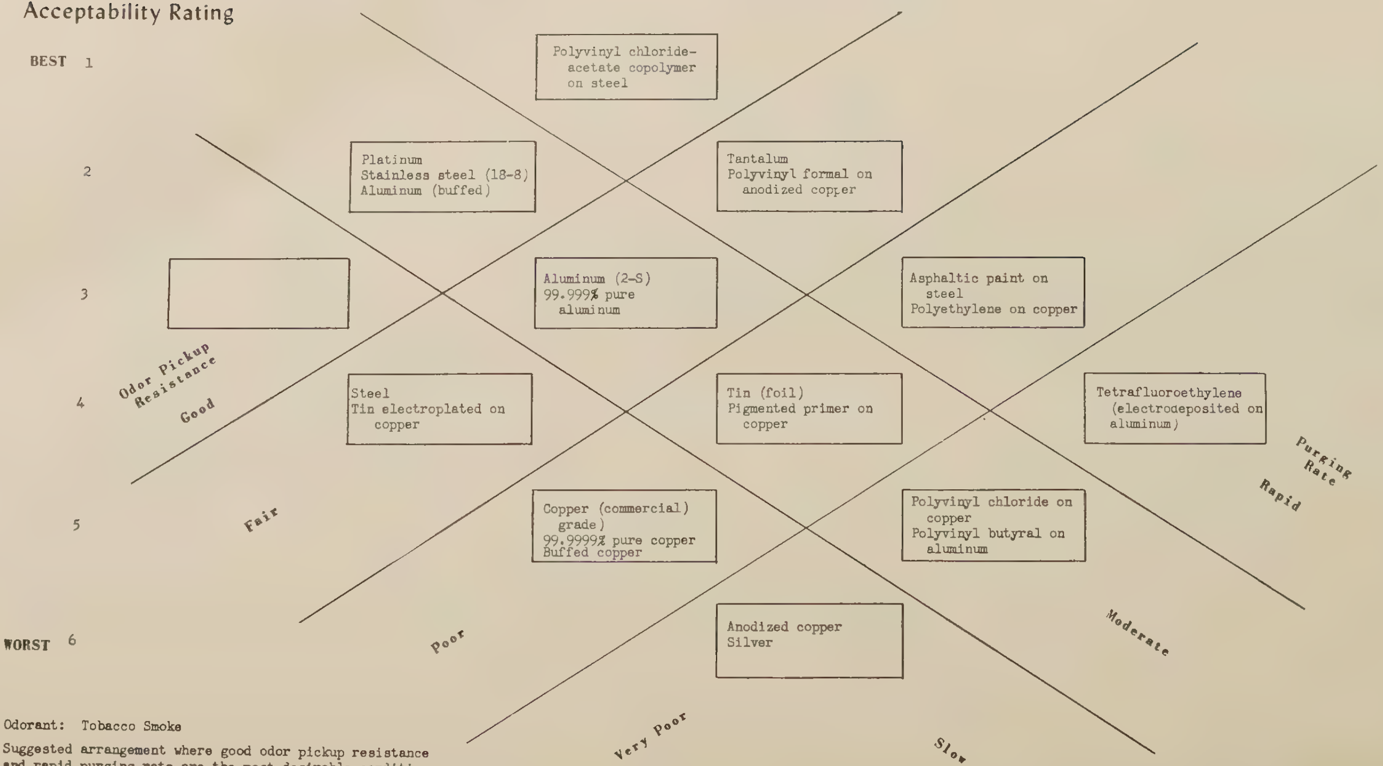
ODOR PICKUP RESISTANCE	SLOW	MODERATE	RAPID
GOOD		Platinum Stainless steel (18–8) Aluminum (buffed)	Polyvinyl chloride-acetate copolymer on steel
FAIR	Steel Tin electroplated on copper	Aluminum (2-S) 99.999% pure aluminum	Tantalum Polyvinyl formal on anodized copper
POOR	Copper (commercial grade) 99.9999% pure copper Buffed copper	Tin (foil) Pigmented primer on copper	Asphaltic paint on steel Polyethylene on copper
VERY POOR	Anodized copper Silver Tantalum vapor-deposited on aluminum	Polyvinyl chloride on copper Polyvinyl butyral on aluminum	Tetrafluoroethylene (electrodeposited on aluminum)

PURGING RATE

Odorant: Tobacco Smoke

TABLE 2

ODOR EVALUATION OF METALS AND COATINGS ON METALS



Odorant: Tobacco Smoke

Suggested arrangement where good odor pickup resistance and rapid purging rate are the most desirable conditions.

forth. By this presentation of the results, six categories of performance, or desirability, from best to worst are indicated.

The highest rated material, polyvinyl chloride-acetate copolymer on steel, is a dramatic example of a coating improving the performance of a material. Polyvinyl butyral on aluminum lowered the rating of aluminum. Both these materials are organic coatings and can be judged as such if their coverage of the base metal is complete. For example, polyethylene on copper oxide upgrades the base metal by increasing the purging rate. This appears to be a function of the coating, completely independent of the base metal, for the same coating on aluminum received an identical odor rating. There are, however, so many variables in the organic coatings, it is not practical at this time to theorize on the mechanisms behind their odor properties.

Nonmetallic Surfaces

A number of nonmetallic surfaces have also been studied and their odor performances and ratings were observed to be not unlike those found in metals. Solid polymerized methyl methacrylate with a highly polished surface fulfills the standards for the nearly ideal material from an odor standpoint.

Cottons and woolens ranged from the ideal Good-Rapid to Very Poor-Slow depending on the type of fiber, weave, and finishing. The performance of synthetics also varied. Rayon-acetate showed fair odor resistance and fast purging. A pile fabric composed of dynel and Vicara was given a very low rating, probably due to the great surface area of the fabric.

Natural rubber, which is usually considered to have a strong odor of its own, has in addition the characteristic of modifying the odor which it retains. Rubber accumulated odor to a high intensity level; and, despite a considerable decrease in odor upon purging, the residual odor had an objectionable character. The nature of these notes caused rubber to rate poorly.

Conclusion

The public today is increasingly concerned with the odor of the products it buys. The fact that items from mattresses to plastics are advertised and labeled as containing deodorants or as being odor-free indicates increasing significance of odor to the consumer. A number of manufacturers are meeting present-day demands of consumers by selecting odor-free raw materials as an aid in the production of odor-free products. But this alone is not enough. Most materials can acquire odor from the atmosphere surrounding them. In many instances the newly acquired odor can act as an odor source and contaminate other materials. This accumulation of odor by surfaces and the subsequent transfer of this odor to other materials form the basis for many industrial odor problems. Change in the nature of odors in the process of adsorption and desorption often leads to confusion as to the responsible source. For example, copper and other metals may selectively release sulfide notes suggestive of stale cooking odors, and yet these odorants may have been acquired from sources totally unrelated to food. Although neither consumers nor manufacturers are as aware of acquired odor as of initial odor, the former is just as serious, perhaps more so because it appears so subtly. Most people have noticed instances of acquired odor—railroad Pullmans and hotel corridors. It is unfortunate that these odors are accepted as part of the world in which we live.

Standard procedures, however, have been developed which enable a manufacturer to determine the behavior of his product in the presence of various odorants with respect to the product's adsorption, retention, and release characteristics. On the basis of special techniques developed for the study of odor transfer, it is often possible to determine the source of unpleasant odors which occur in a wide variety of materials and media. Such judgments are facilitated by modification of the flavor profile procedure.

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OBSERVATIONS ON OLFACTORY INTENSITY. I. TRAINING PROCEDURE, METHODS, AND DATA FOR TWO ALIPHATIC HOMOLOGOUS SERIES*

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Olfactory intensity has long been a problem of interest. Both technique and procedure for assessing olfactory intensity have had years of development in the laboratories of universities, industry, and governmental agencies. Wenzel[9] has reviewed the technical aspects of the problem. Beck,[2] in reviewing procedure, suggested applying psychophysical scaling methods to odor. These procedures grew out of the pioneer work of Allison and Katz,[1] and Crocker and Henderson.[4]

Toward the Specification of the Problem

Fundamentally the results presented in this study came about as a result of trying to do for smell intensity what Fletcher and Munson did for sound intensity and what many pioneers did for heterochromatic photometry. Fletcher and Munson asked subjects to match the psychological intensity of a 1000 cycle tone to the psychological intensity of a tone of any other frequency. The physical intensities of the many matches their subjects made were not necessarily equal. But the set of tones which were matched to a given intensity of the 1000 cycle tone were all tones of equal loudness. Abney, for one, had subjects match the brightness of a standard "white" light to the brightness of some colored lights. The inverse square law, or the aperture, or the filter thickness enabled him to say that a certain red or green or blue or yellow light was equal to his standard light.

Our problem was analogous. We picked a standard odorant and prepared a set of diluted solutions of the standard. These were placed in uniform test tubes. They gave us a scale of odorous intensity that was physically anchored in terms of the concentrations of the standard. This set of standards is as reproducible as Fletcher and Munson's standard 1000 cycle tone and as reproducible as a standard lamp. Odor intensity is varied by varying concentration. Loudness is varied by an attenuator and brightness by the inverse square law. Still the fundamental fact is that all three: loudness, brightness, and odorous intensity are anchored to duplicable standards.

The problem we gave our subjects was that of finding a concentration of a standard which was as strong as a comparison odor differing in quality. The experiment was designed to get a factual answer to five questions: (1) Can subjects make the judgment? (2) If they can, how consistent are they in repeated trials? (3) How do subjects agree and disagree with each

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* This research was supported by funds partly from the Research Corporation and partly from the Department of Psychology.

other? (4) How does odorous intensity vary as a function of the concentration of a comparison odorant? (5) How does odorous intensity vary in aliphatic homologous series?

Apparatus, Experimental Methods and Procedures

The technical aspects of the experiment concern: (1) the standard odorant and its accessory diluent apparatus and procedure, (2) the comparison odors, and (3) the psychophysical procedures including the training of the subjects.

The preparation of the standard odor series. Sniffing through an odor library led to the preliminary judgment that aldehydes produced more intense olfactory sensations than any others on the shelf. The communality of this experience was confirmed by the independent judgments of ten other people. The group of ten sniffed a set of aliphatic aldehydes C_5 to C_{13}. Nine of the ten ranked heptanal strongest; the other subject chose heptanal second—undecanal was first. The odorous power of heptanal made it possible to study a wide range of compounds in their maximum odor strength, as undiluted compounds. While mercaptans might be stronger, we hesitated to find out because we were working in a building with other people.

The standard of odorous intensity having been chosen, the problem of choosing the diluent remained. Its desirable characteristics, organically universal as a solvent, relatively unreactive, and nearly odorless have been listed.[3] Benzyl benzoate and diethyl phthallate seemed good in preliminary solubility and reactivity searches of the literature and laboratory tests. Others were tried: dibutyl phthallate, dicapryl adipate, butyl stearate, dioctyl phthallate, didecyl ether, and dibutyl sebacate, but these had strong odors which varied from lot to lot and from manufacturer to manufacturer. The extraneous odors were probably processing impurities. Mallinckrodt's Benzyl Benzoate, USP XIII, 3872 control TSN-1 was chosen. It is low in odorosity as is attested by its Crocker-Henderson numbers. Diethyl phthallate was rejected because some subjects said that it made their noses sting. (Possibly this property is what makes it satisfactory as an insect repellant.)

Polak's Frutal Works heptanal was chosen as the standard. Two samples, one from Middletown and one from Amersfoort had identical odors. Such duplicability assured us of a uniform standard. Furthermore, while the lots run from 97 to nearly 100 per cent pure aldehyde, the odors of whatever impurities may be present have little chance of being smelled because of heptanal's powerful odor. Besides there is some experimental evidence showing that masking does not decrease odor intensity but merely reduces the chances of smelling an odor.[2]

The procedure for preparing the heptanal-benzyl benzoate series was as follows: one cc. of heptanal was pipetted into a new 10 mm. by 75 mm. test tube (Kimble #45050) by means of a delivery pipette. This was the 100 per cent standard. That test tube was stoppered with a fresh cork from a recently opened bag (Armstrong XXXX, regular, No. 0). One cc. of heptanal was pipetted into a second test tube. One cc. of benzyl benzoate was added to the heptanal in test tube two. A clean pipette was used to mix the solution by sucking the tube contents in and out of the pipette five times. One cc. of the mixture was transferred to a third test tube. Test tube two was stoppered. It formed the second member of the standard series. One cc. of benzyl benzoate was added to test tube three. One cc. of the mixture in test tube three was transferred to a fourth test tube. Tube three was stoppered; it contained ¼ heptanal and ¾ benzyl benzoate. The procedure was continued for tube four which was ⅛ heptanal, for five which was 1/16, and so on until a series of 19 tubes had been assembled. For convenience, the series of dilutions by volume is assembled in TABLE 1 to show the fact that it forms a geometric series and to provide a convenient reference table for those who may be interested in considering the data from other points of view.

TABLE 1

Tube No.	*Heptanal Fraction*	*Heptanal Attenuations* $-\text{Log}_2$ *(Heptanal Fraction)*
0	1/1	0
1	1/2	1
2	1/4	2
3	1/8	3
4	1/16	4
5	1/32	5
6	1/64	6
7	1/128	7
8	1/256	8
9	1/512	9
10	1/1024	10
11	1/2048	11
12	1/4096	12
13	1/8192	13
14	1/16384	14
15	1/32768	15

TABLE 1 defines the numbers appearing on the axis of ordinates of the graphs which present our results.* The tubes represented by these numbers were placed on a board 1¾″ × 20″ × ¾″ with holes 7/16″ in diameter arranged linearly one inch between centers in the middle of and lengthwise down the board. This test tube rack was centered on and fastened to a base ½″ thick and ½″ larger over-all than the rack board. Several of these racks were made to accommodate the standard as well as the comparison odors.

The comparison odors. The comparison odors used were the aliphatic alcohols, butanol (C_4) through (C_{12}), duodecanal and the acetate esters (C_6) hexyl through duodecyl (C_{12}). The alcohols were arranged in a dilution series like heptanal but only to an attenuation of 6 because dilutions exceeding that approached odorlessness. Methyl, ethyl, and propyl alcohol were not used because of the great difficulty of obtaining them in pure form and because of their irritant action, which Passy[7] discusses.

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* Due to a drafting error all of the attenuations on the graphs are one unit higher than they should be.

Comparison odors other than the alcohols and acetates could have been used; these were selected because they formed homologous series and because the procedures by which they were synthesized and purified are duplicable. But a beginning has to be made somewhere and the initial choice of odorants is historically conditioned by the work of Passy, Zwaardemaker, Crocker and Henderson, Parker, Crozier, and Dethier. All studied behavior with respect to homologous series.

Subjects and procedure. Some of the problems encountered in training subjects have been listed. For the most part they consist of familiarizing the subject with the details of the experimental situation, answering his questions, but calling his attention to the relevant variables. But much is unverbalized: we don't know how to tell him to sniff. We have to rely upon the stability of the sniffing habits he has built up over the years of his life or upon new habits he learns in the course of training. All that can be hoped for is a stable sniff. But we need not rely on mere hope, for if a subject returns data on one day which agree with that of another day's work, then we can assume that he sniffs the same way each time. While it might be true that his absolute sensitivity might change, it is a reasonable hypothesis that his relative sensitivity might not change and thus render the form of the data invariant. Such is the case in the data of vision and audition. The variables that determine visual thresholds have been listed in part. They are some sixty. They can be translated appropriately for olfaction. But they are not meaningful unless they can be manipulated experimentally. Nevertheless, if a subject reproduces his own data, the constancy of the variables determining his olfactory behavior can be assumed. The work of Crocker and Dillon shows that quantitative judgments can be made.[10]

The present study then takes the sniffing habits that people possess and attempts to determine the stability of those habits in terms of the concentrations he judges equal in intensity. An older way of looking at the problem would view this study as determining whether the sensitivity of the olfactory sense cells was constant. But the psychologist deals with the total man.

Before examining the data in order to assess the stability of olfactory habits, let us summarize the procedure in relation to the way the results are presented. The data were obtained from four subjects over an observation period of five months. No more than one homologous series of a given dilution was compared to the heptanal standard in a given session. The one to 18 day interval between sessions was introduced to obviate any specific odor learning. An exception is the acetate series where one day elapsed between sessions. The data of each series (FIGURES 1 to 10) were obtained in two months. Thus each line connecting the points in each figure represents one day's work. The points on the first ten figures represent a single determination. It should be pointed out that the comparison odors were presented in random order to the subjects.

Results

The results are presented graphically in FIGURES 1 to 12. FIGURES 1, 2, and 3 present the data of three untrained subjects obtained when they compared the intensity of the 100 per cent alcohols (attenuation zero) with the heptanal standard. The number of carbon atoms in the aliphatic alcohol molecule is plotted on the abscissa. The ordinate gives the heptanal attenuation or dilution which the individual subjects chose as corresponding in intensity to a particular alcohol. To repeat, each point is a single judgment. Inspection of these graphs shows that a subject makes intensity matches which agree when made a month apart. There are variations but these data are about as duplicable in form as those of vision and audition. From these graphs we conclude that a subject can reproduce his own data even when the comparison odors are presented in random order.

FIGURE 4 presents the averaged data of FIGURES 1, 2, and 3. This graph was drawn to determine the consistency from subject to subject. Two subjects are alike; one is different. There is general agreement in form except for decanol and undecanol. The anomalies in the graphs at C_{11} may be real.

FIGURES 5, 6, and 7 present the data for the same three subjects, taken as before but with them sniffing 50 per cent alcohols (attenuation is 1). The data again show agreement individually. One subject (FIGURE 5) maintains his alcohol differences. The peculiarity at C_{11} is not stable.

FIGURES 8, 9, 10 show individual agreement when the aliphatic acetates, hexyl (C_6) through duodecyl (C_2), are compared with the heptanal standard. As in the previous figures, each point represents a single reading. The agreement is excellent individually, but only two subjects show even fair agreement in form. Again we find an anomaly at C_{11}.

In summary, covering the first ten figures, we can say that a subject makes reproducible intensity matches and that subjects show some general agreement with each other. There are peculiarities which appear fairly consistently but their meaning is not clear. The C_{11} peaking is one such—there may be a trace impurity; there may be physiological reasons. The data present a problem.

In comparing the curves for the 50 per cent alcohols and the 100 per cent alcohols, one notices a general tendency for the 50 per cent alcohols to be lower than the 100 per cent alcohols. There is no *a priori* reason for expecting such a finding, although one might be misled into thinking there is a one to one correspondence between concentration and intensity. In general the more concentrated a solution the greater is its odorous intensity.[1,2,6,9] But a curve plotting psychological intensity, *odorosity* (a word we suggest for the intensive dimension of odors), has to be worked out for each odorant. One might make the mistake of a judge who insisted upon opening a bottle of natural gas odorizing agents in a courtroom over the protests of a representative of the company who manufactured the product. The judge opened the bottle, sniffed, and passed it to the jurors to sniff. Everyone agreed that it was not a strong odor. The bottle was capped as Exhibit

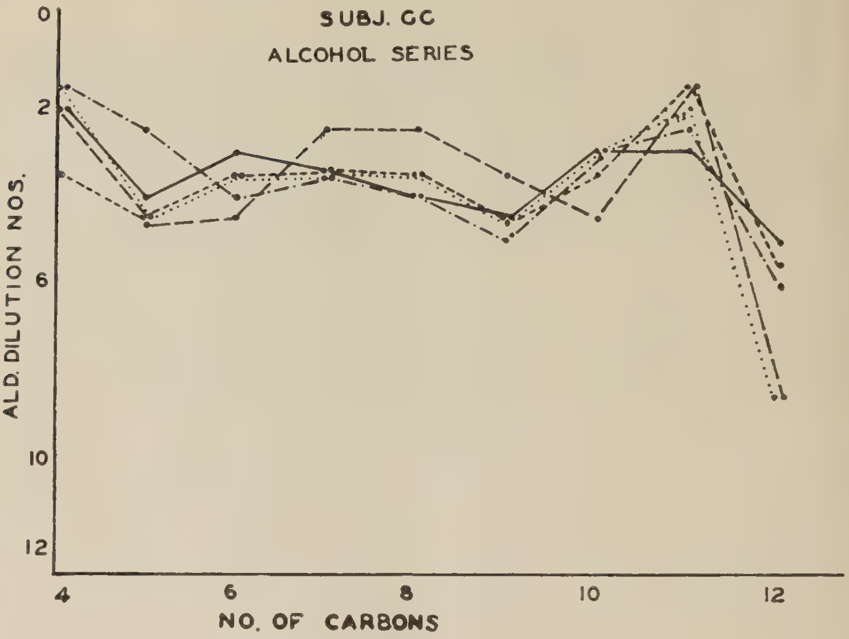


Figure 1.

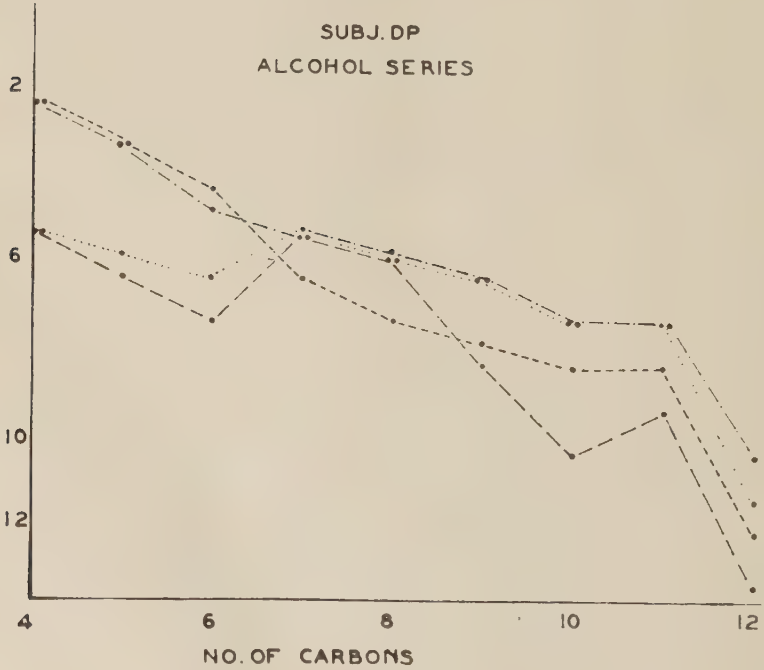


Figure 2.

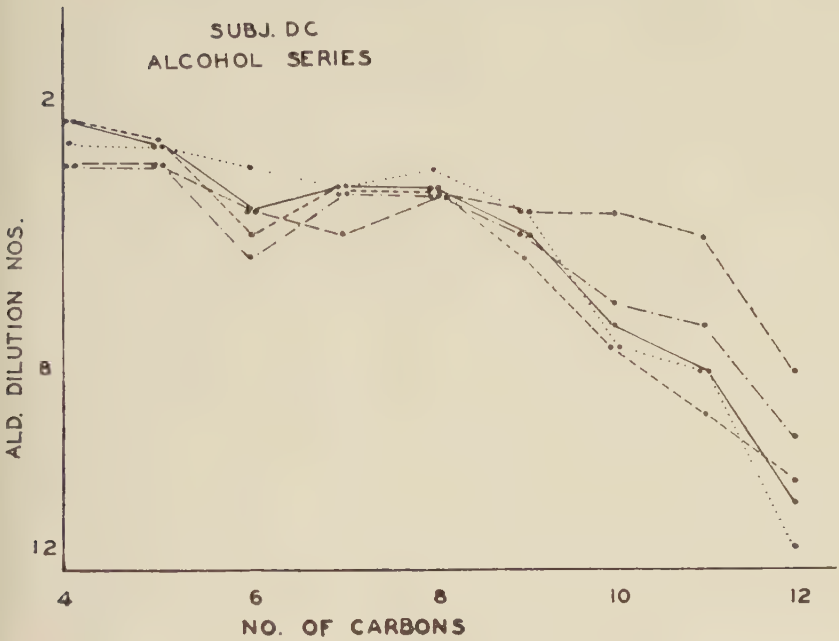
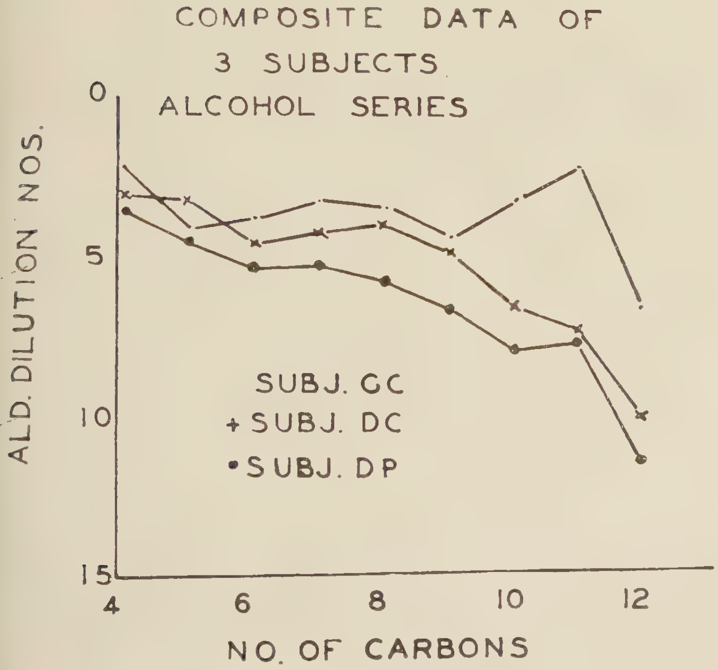


FIGURE 3.



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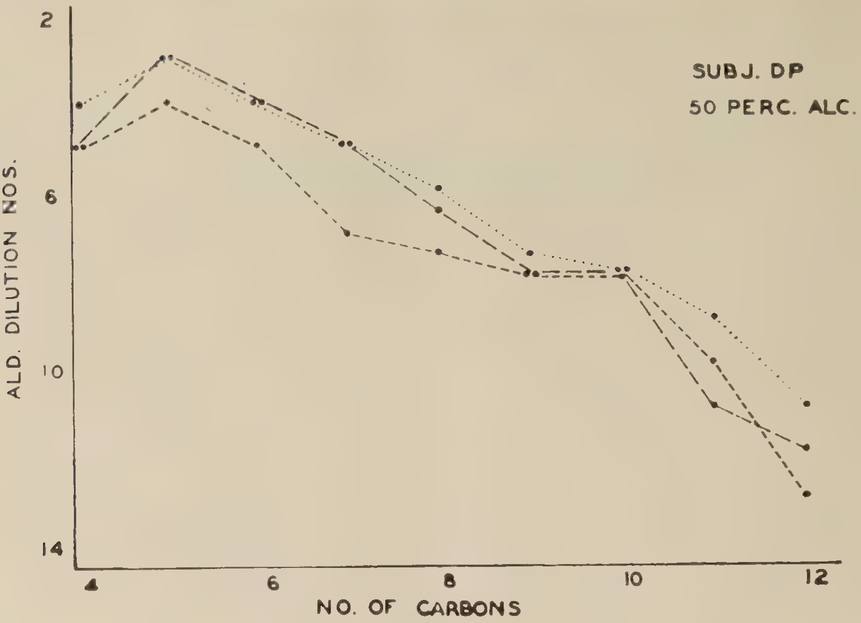

Figure 5.

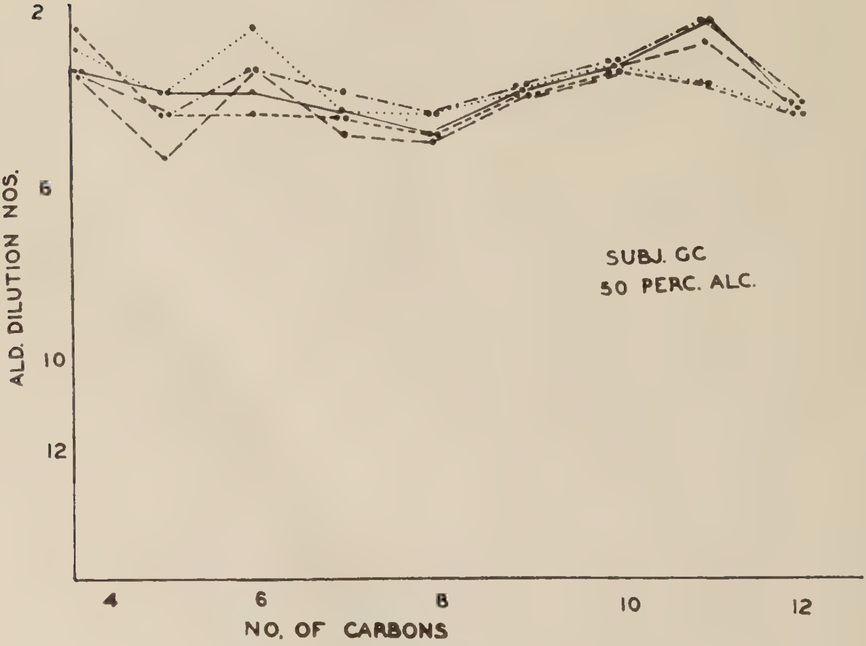

Figure 6.

A. The court was adjourned for lunch. When court reconvened, the stench was so overpowering that the judge had to clear the courtroom for three days. Our inference is that the mercaptans may have a *maximum* of odorosity as a function of concentration.

While the alcohol series already run might yield data on the relation

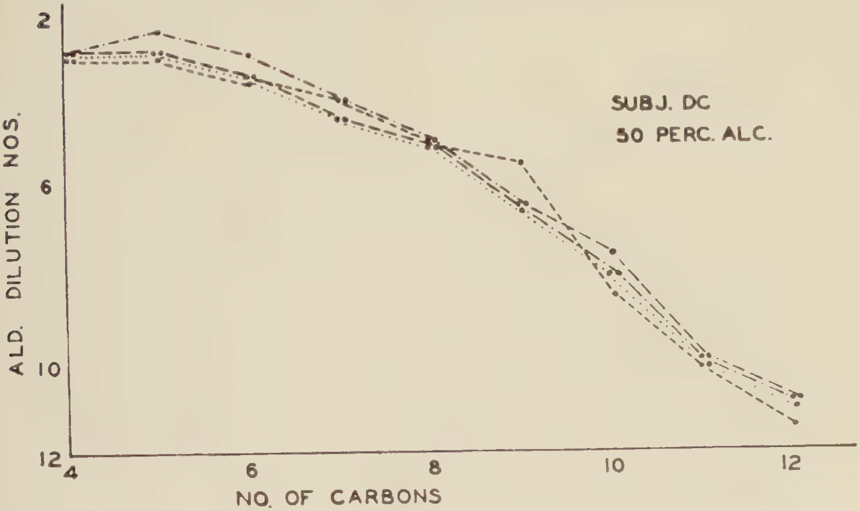

Figure 7.

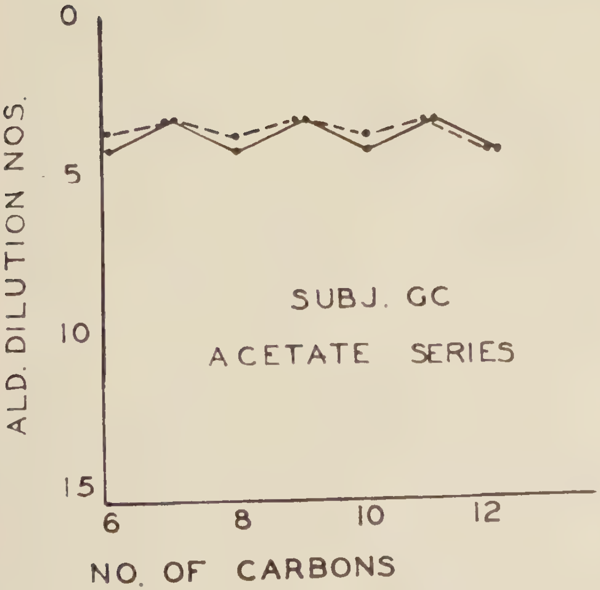

Figure 8.

between odorosity and concentration, it is more scientific to run a separate experiment where different concentrations are compared on the same day.

FIGURE 11 presents the data for the alcohol series at attenuations of 1, 2, and 3. Each point is the average of eight odorosity matches. The data

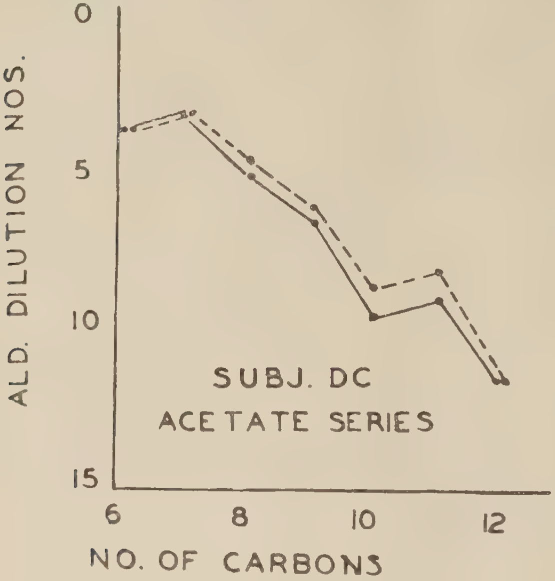

FIGURE 9.

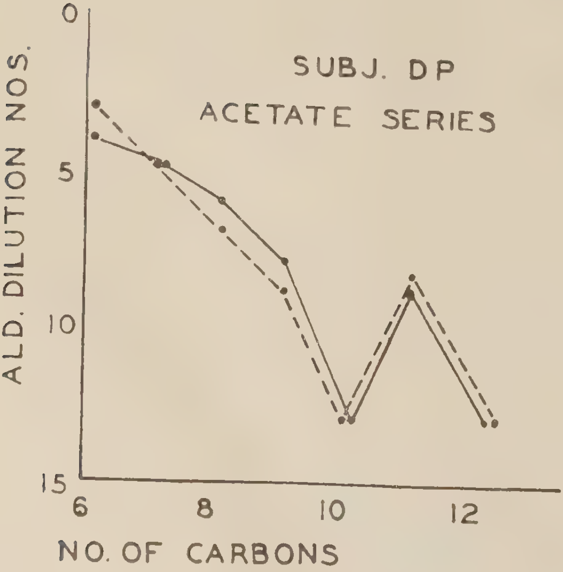

FIGURE 10.

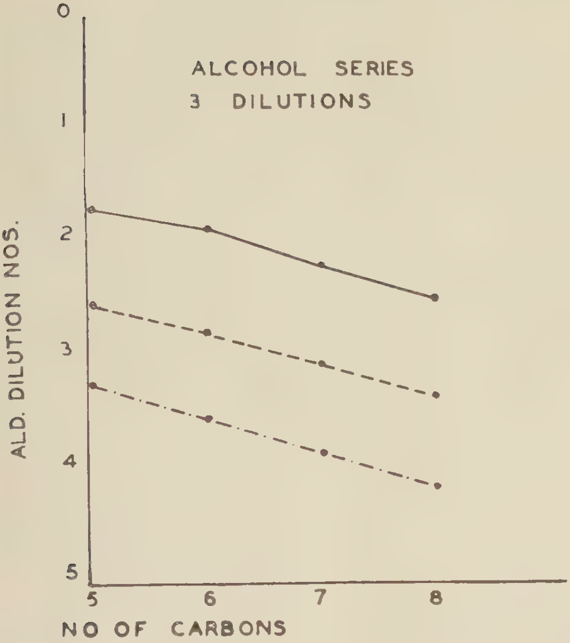

FIGURE 11.

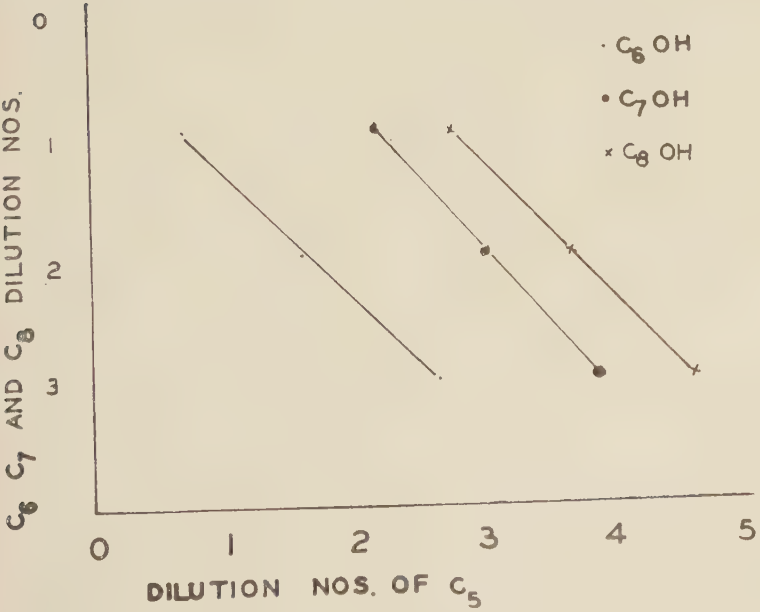

FIGURE 12.

were obtained under the following conditions: (1) No two judgments took place within five minutes of each other and were often made at intervals of thirty minutes; (2) The total work was spread over a period of three hours (the subject interspersing the judgments with other work); (3) The subject previously learned to order the alcohols according to concentration when his sole cue was odor, a procedure which took ten training sessions. These conditions control the problem of adaptation and test whether the subject can respond to the relevant cue of intensity. The heptanal-alcohol odorosity matches of FIGURE 11 are elegant and show what a well-trained subject can do. But for generality we need more information or more noses sniffing more compounds. The scientific gains are well worth the time spent.

This same subject used pentanol as a standard to match the odorosity of hexanol, heptanol, and octanol, each in three attenuations, 0, 1, and 2. These data are presented in FIGURE 12. They were obtained in the same way as the data of FIGURE 11, but each point summarizes four days' work instead of eight. The dilutions of the comparison odors are plotted on the ordinate, those of the pentanol "standard" on the abscissa. Comparison of FIGURES 11 and 12 confirms the decrease in intensity with decreasing concentration and with increasing chain length when either heptanal or pentanol are used as standards.

Those last two graphs can be used to ascertain whether the agreement between one standard and another is quantitative. Horizontal lines in FIGURE 11, and vertical lines in FIGURE 12 define iso-odorosity levels. From the spacing of the observed lines we can estimate the dilution of the various alcohols which are at the same odorosity levels. These computations are presented in TABLE 2.

TABLE 2
DILUTIONS OF EQUAL ODOROSITY

	Comparison odors			
Standard	*Pentanol*	*Hexanol*	*Heptanol*	*Octanol*
Heptanal	2.60	1.78	1.28	1.00
Pentanol	2.70	3.10*	1.64	1.00
Heptanal	3.20*	2.71	2.30	2.00
Pentanol	3.70	4.10*	2.73	2.00

The starred values were obtained by linear extrapolation.† The others are interpolated except octanol which was arbitrarily constrained at dilutions of 1 and 2.

One cannot say whether the data show quantitative agreement or not, for only pentanol and heptanol can be legitimately compared since octanol odorosity was arbitrarily fixed and hexanol has extrapolated values. The problem is an experimental one. Heptanal and pentanol are different scales and their transformation graph has to be determined by direct comparison through several scale points. That is another research problem.

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† Research in progress indicates that linearity is not maintained. This may account for the discrepancy.

Let us summarize our results as they answer the specific questions we asked in this experiment.

(1) Subjects can make quantitative odorosity matches.

(2) They are consistent in repeated trials.

(3) In broad trends the data of one subject agrees with the data of another subject, as well as sensory data on loudness and direct heterochromatic photometry. But it should be pointed out that there are no odor norms. These data are a start toward that goal.

(4) Odorosity decreases with increasing dilution for the compounds studied.

(5) Odorosity decreases as a function of increasing chain length for the acetates and alcohols studied, with minor exceptions.

Discussion

The result that odorous intensity decreases as a function of chain length agrees with Passy's data[3] on threshold. If we add the FACB numbers in Crocker and Henderson's Figure I for the aliphatic alcohols,[4] we obtain a plot that follows the contours of our data, even reproducing the peak at undecanol. This suggests an interesting problem: Are the Crocker and Henderson "whiff numbers" additive in producing an over-all estimate of odorous intensity? Our findings neither agree nor disagree with the finding of von Hornbostel[5] that odor "brightness" increases with increasing chain length. For von Hornbostel did not mean by odor brightness what we mean by intensity. He specifically said that brightness was different from intensity. ". . . dass die Gerüche ausser Intensität (Lautheit) und Qualitäten (Farbe) auch noch Helligkeit haben, musste erst entdeckt Werden," and again, "Nachdem Vorversuche gezeigt hatten, dass Gerüche sich, abgesehen von ihrer Qualität und Stärke, leicht und sicher nach ihrer Helligkeit vergleichen und ordnen lassen, ergab sich die Frage, ob nicht vieleicht zwichen der phänomenalen Helligkeit und der chemischen Constitution gesetzmässige Beziehungen bestehen." Brightness is another dimension of odors which anyone can learn by sniffing the compounds von Hornbostel ordered according to his concept of brightness.

Moncrieff's ordering of the alcohols[6] with nonyl as the most intense may depend upon his subjects, and upon his compounds and the way they were prepared. These are experimental differences that are easily settled by an exchange of materials. These are problems of standardization. At this stage no one is right or wrong; information is being gathered. Techniques have to be developed, and the nature and range of relevant variables that are related to odorous intensity have to be determined.

Perhaps intensity is a complex of sensations from the trigeminal nerve endings in the nose that make some substances possess not only odor, but also taste, cold, warm, pain, and contact properties. Research will tell.

Summary

A technique for measuring odorous intensity is described. The results show agreement both within and between individuals. There are individual differences.

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Part IV. Experimental Studies in Odor

SURFACE PHENOMENA RELATED TO ODOR MEASUREMENTS

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The importance of an objective method of odor measurement is well recognized. Such a technique would eliminate physiological and psychological factors present, very prominently, in subjective test methods. An objective method of measurement which would permit quantitative and qualitative measurements would be of great value, particularly if it permitted measurements below the threshold level of the human nose. Instruments of such general character are available in the field of optics and in the field of acoustics. If a suitable transducer can be developed, the measurement of odors might be done by electric circuit methods using the advanced technique of electrical measurements.

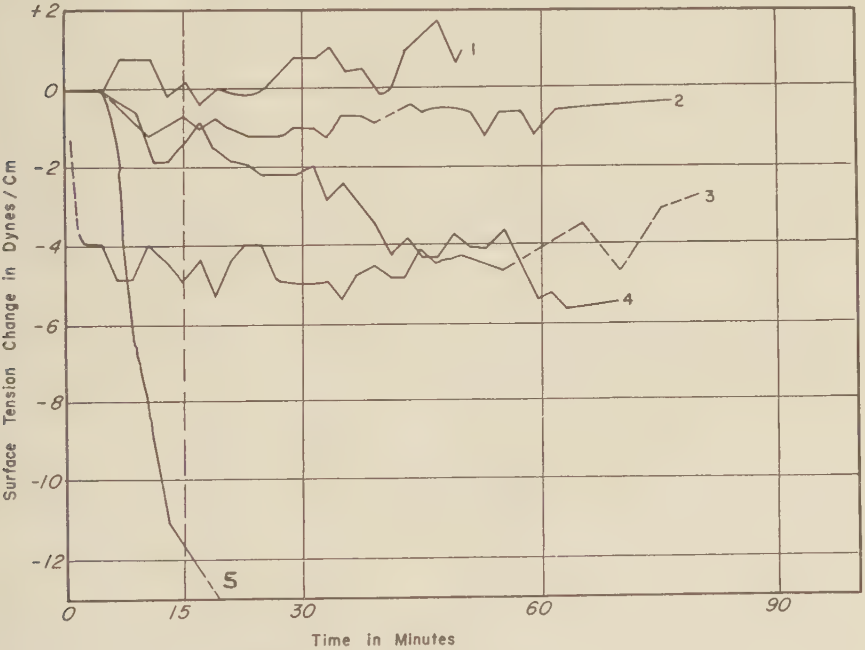

FIGURE 1. Effect of contaminant on surface-tension change. Test liquid: distilled water. Contaminant in box: 1. Iodoform; 2. moth balls; 3. rubber; 4. cloves; 5. gum camphor.

The long-range objective of the odor investigations made at Purdue University has been to develop electrical means of measuring and classifying

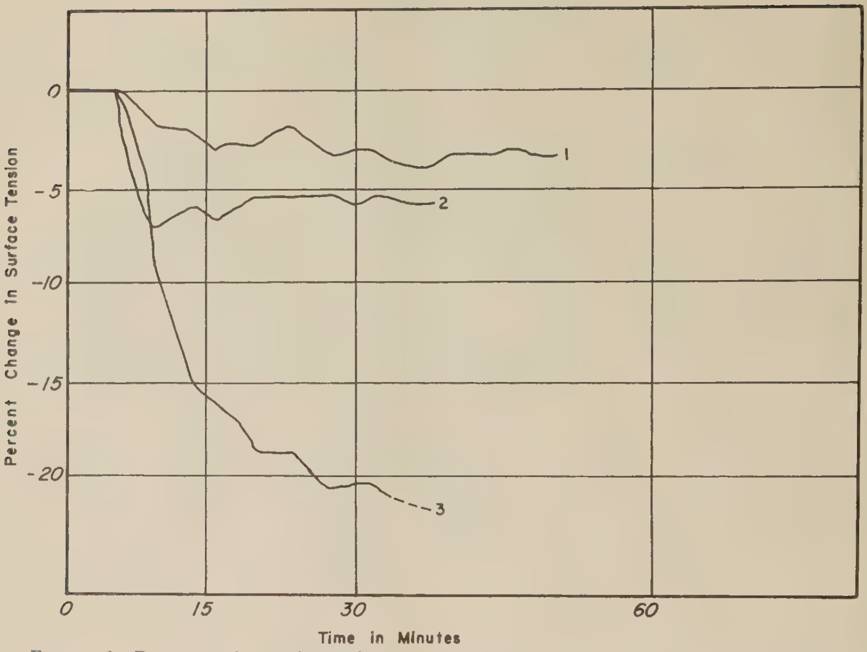

FIGURE 2. Per cent change in surface tension. Contaminant: gum camphor. Test liquids: 1. Mineral oil; 2. mercury; 3. distilled water.

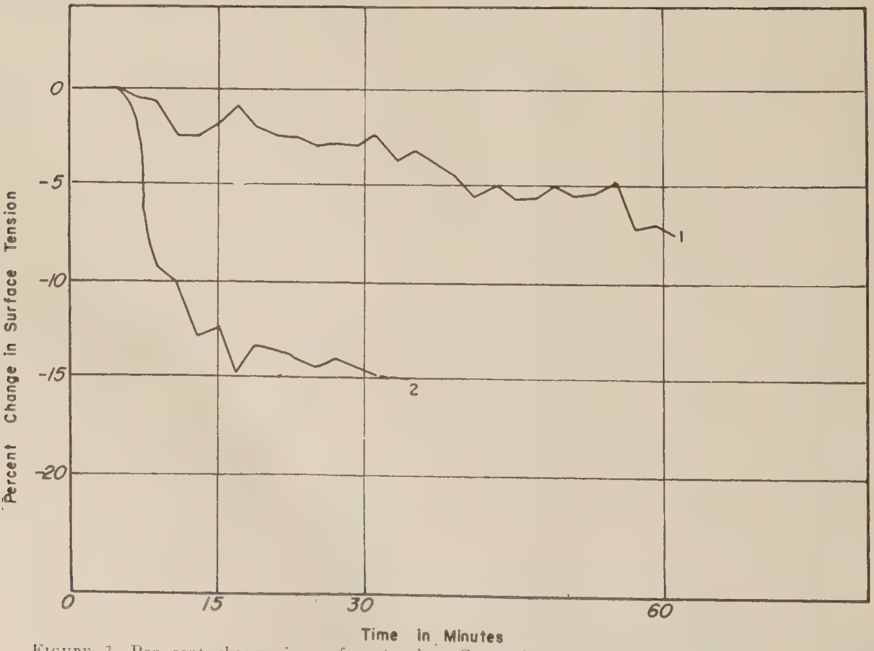

FIGURE 3. Per cent change in surface tension. Contaminant: cloves. Test liquids: 1. Distilled water; 2. mercury.

odors. Recognizing that the human nose may not be capable of detecting all odors, the approach has been to define odors as minute air contamination, whether or not detectable by the human nose. The problem is then one of identifying and measuring air contamination, preferably by electrical methods. Although the attainment of the ultimate objective is far distant, some progress has been made. A nonelectrical method for determining the relative concentration of certain known odorous materials has been developed.

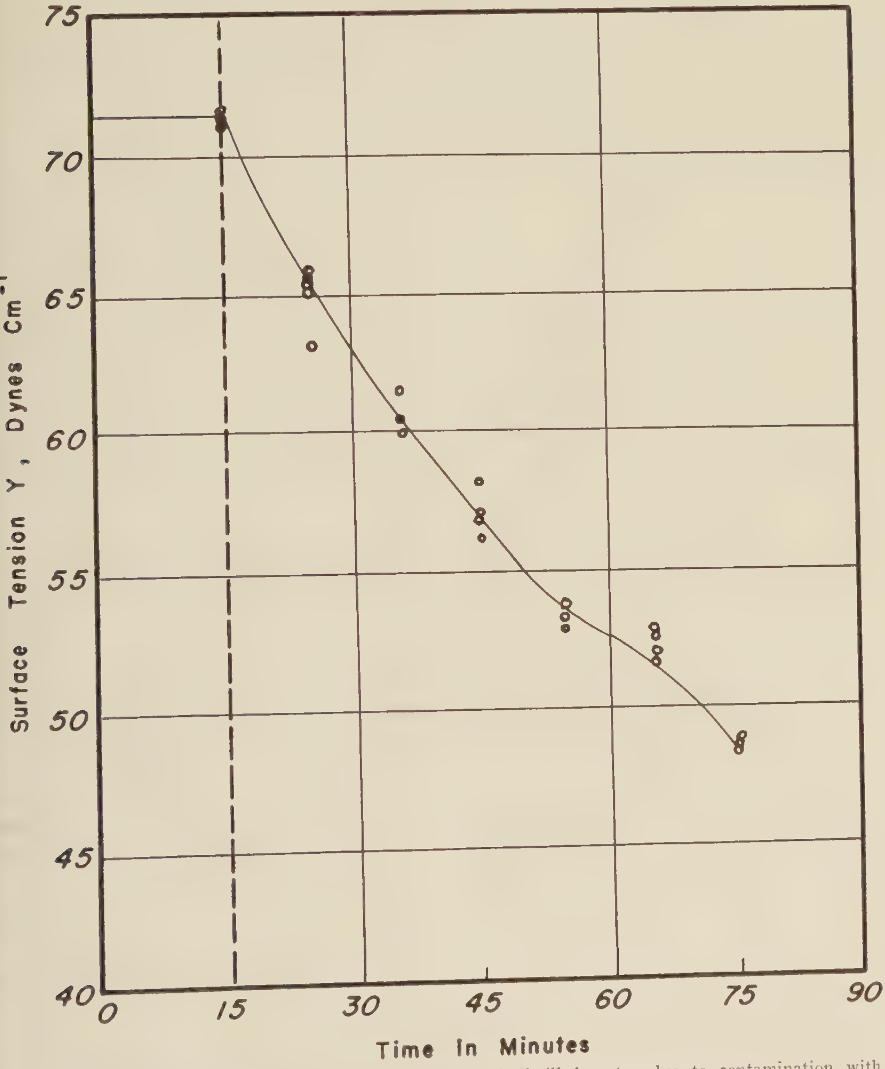

FIGURE 4. The lowering of the surface tension of distilled water due to contamination with eugenol. Five separate tests.

The technique has been applied in the evaluation of the efficiency of certain deodorants.

Minute contamination of the air is known to cause large percentage changes in certain phenomena, among which are:

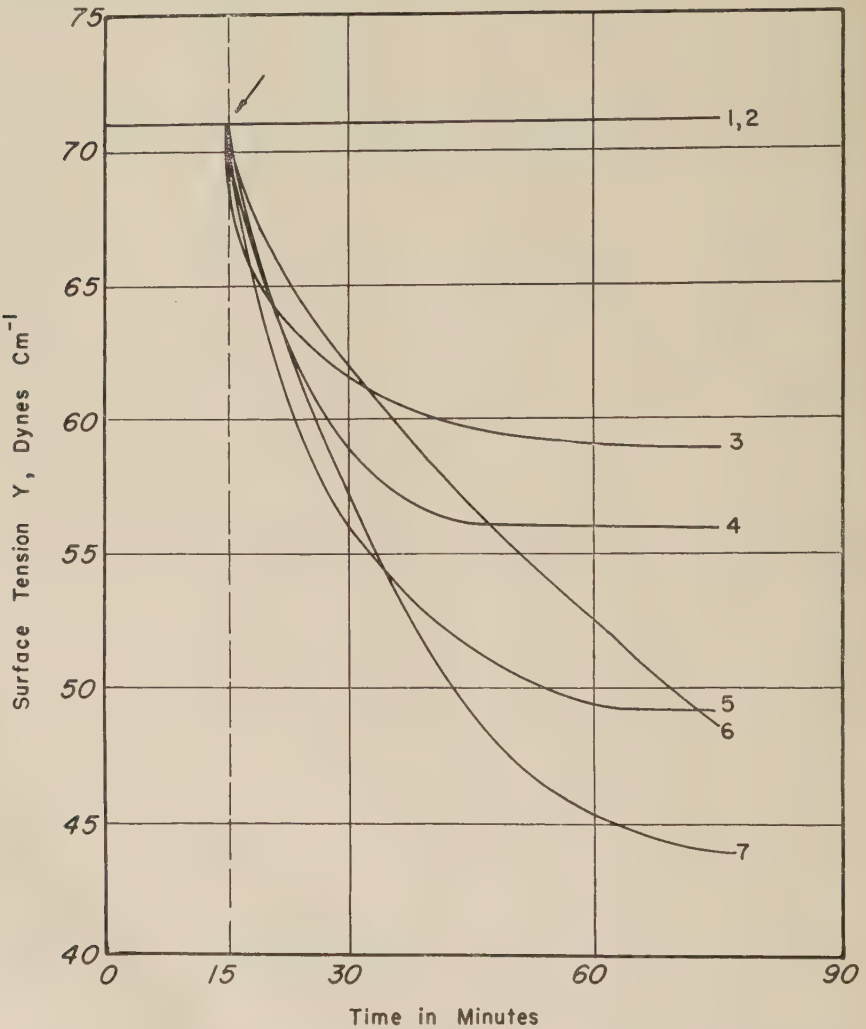

FIGURE 5. The effect of deodorants on eugenol solution. Distilled water drop. 1. Chlorophyllins 1.0 gm.; 2. chlorophyllins 0.75 gm.; 3. charcoal 0.1 gm.; 4. chlorophyllins 0.5 gm.; 5. chlorophyllins 0.1 gm.; 6. eugenol without deodorant; 7. talc 0.1 gm.

(1) The surface tension of liquids in contact with the air;
(2) The emission of electrons or positive ions from heated surfaces; and
(3) The surface potential of liquids and solids.

All of the above are classified as surface phenomena; that is, they are influenced by the characteristics of the outer molecular layers adsorbed on the surface of the body. A study of surface changes and their measurement is the principal subject of this paper.

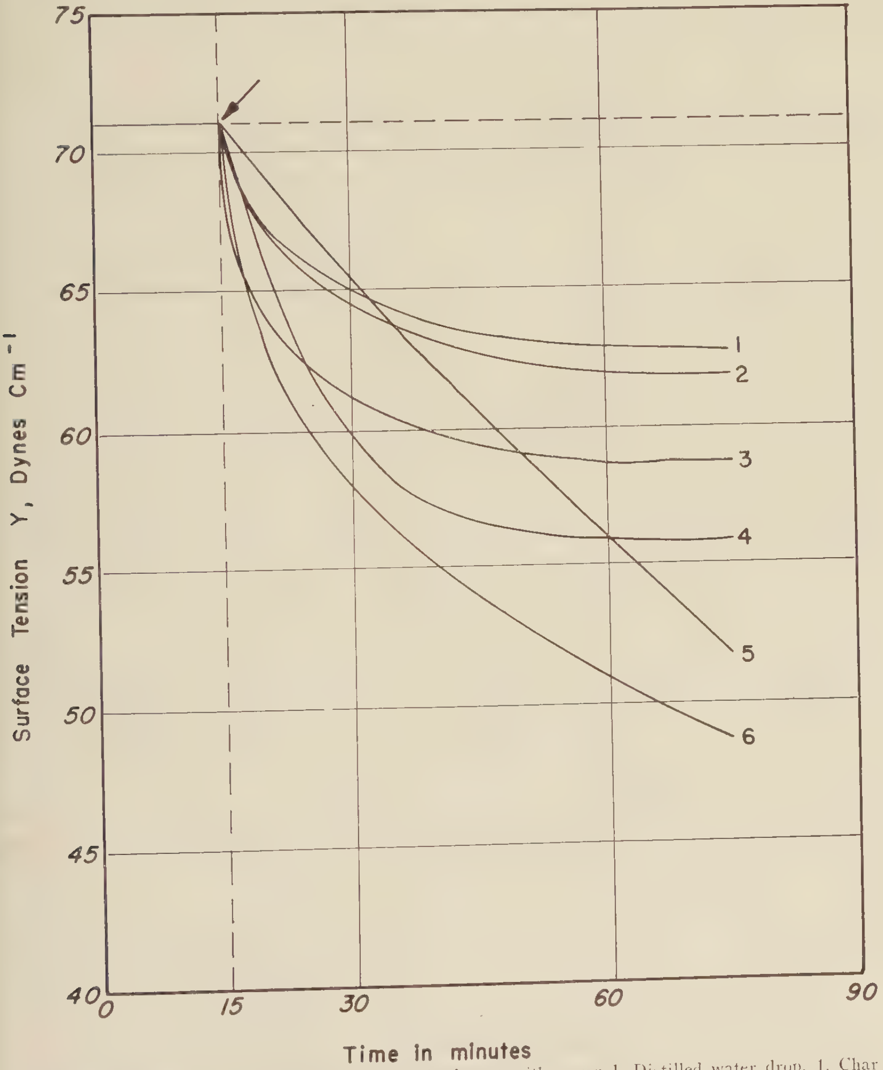

FIGURE 6. Effect of time of contact of the deodorant with eugenol. Distilled water drop. 1. Charcoal 0.1 gm. 60 min.; 2. chlorophyllins 0.5 gm. 60 min.; 3. charcoal 0.1 gm. 15 min.; 4. chlorophyllins 0.5 gm. 15 min.; 5. eugenol solution shaken 60 min.; 6. eugenol solution shaken 15 min

Many investigators have reported on the effect of air contamination on surface phenomena. In practically all such discussions, this effect has been considered undesirable and attempts are made to minimize changes due to air contamination. In relation to the study of odors, however, it is proposed to use these changes as a measure of the degree of contamination of the atmosphere. The general technique of measurements so far developed restricts the evaluation of air contamination by this method to that produced by known contaminating materials. A liquid surface is exposed to the atmosphere within a closed container, into which may be introduced an odorous agent. By use of the pendant drop method of surface-tension measurement, it is possible to make repeated observations of surface tension without disturbing the liquid surface.[1] A value of surface tension may be

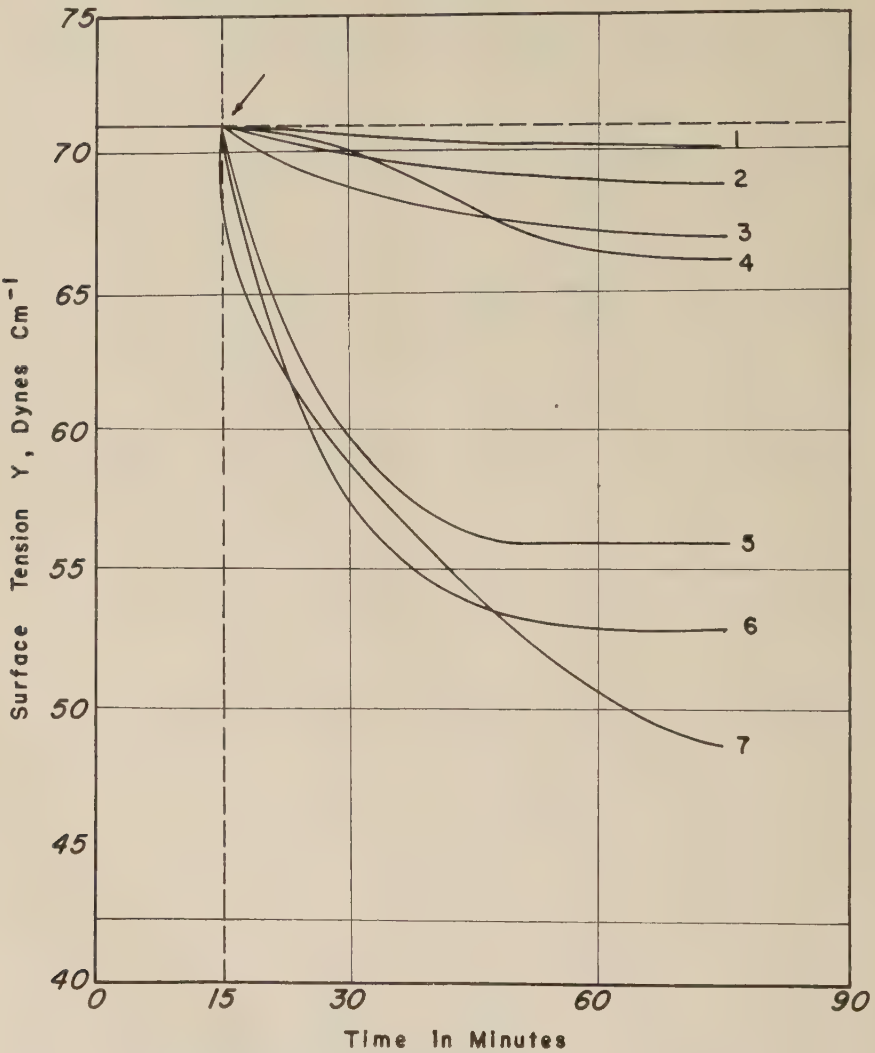

FIGURE 7. Effect of chlorophylls on eugenol solution. Distilled water drop. 1 6. Several different commercial chlorophyll samples; 7. eugenol samples alone.

determined from measurement of photographs of the pendant drop, or by direct measurement of a projected image of the drop. In the majority of studies, surface tension is observed to change with time, decreasing to some stable value in 30 to 60 minutes. The results of tests are usually displayed as surface tension *versus* time curves.

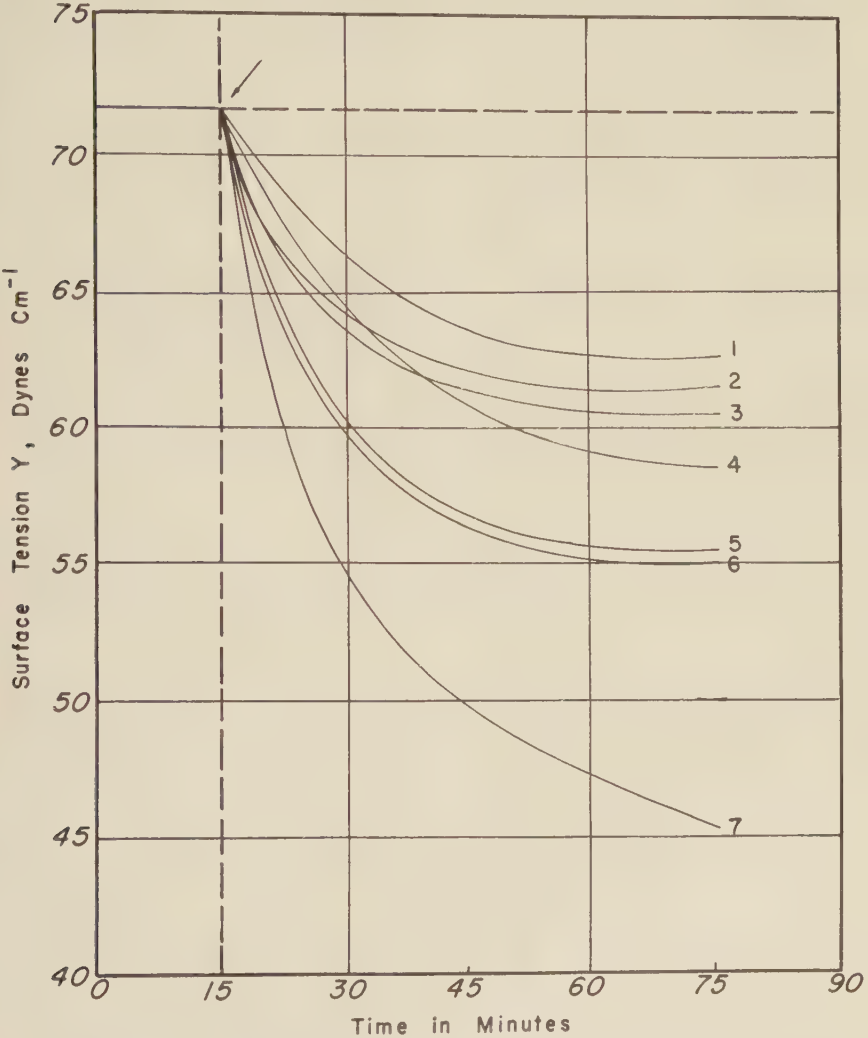

FIGURE 8. Effect of chlorophylls on cineole solution. Distilled water drop. 1–6. Several different commercial chlorophyll samples; 7. Cineole solution alone.

Some typical curves showing the effect of air contaminants on a distilled-water surface are shown in FIGURE 1. As may be noted, gum camphor placed within the container causes a marked reduction in surface tension, whereas moth balls produce very little change. It is readily demonstrated that for a particular contaminant and a particular liquid, the rate of decrease of surface tension depends on the container size and the area of the contaminating material freely exposed. As would be expected, the larger the container, the lower the rate of change of surface tension; whereas, increasing the area of exposed contaminant increases the rate of change of surface tension.

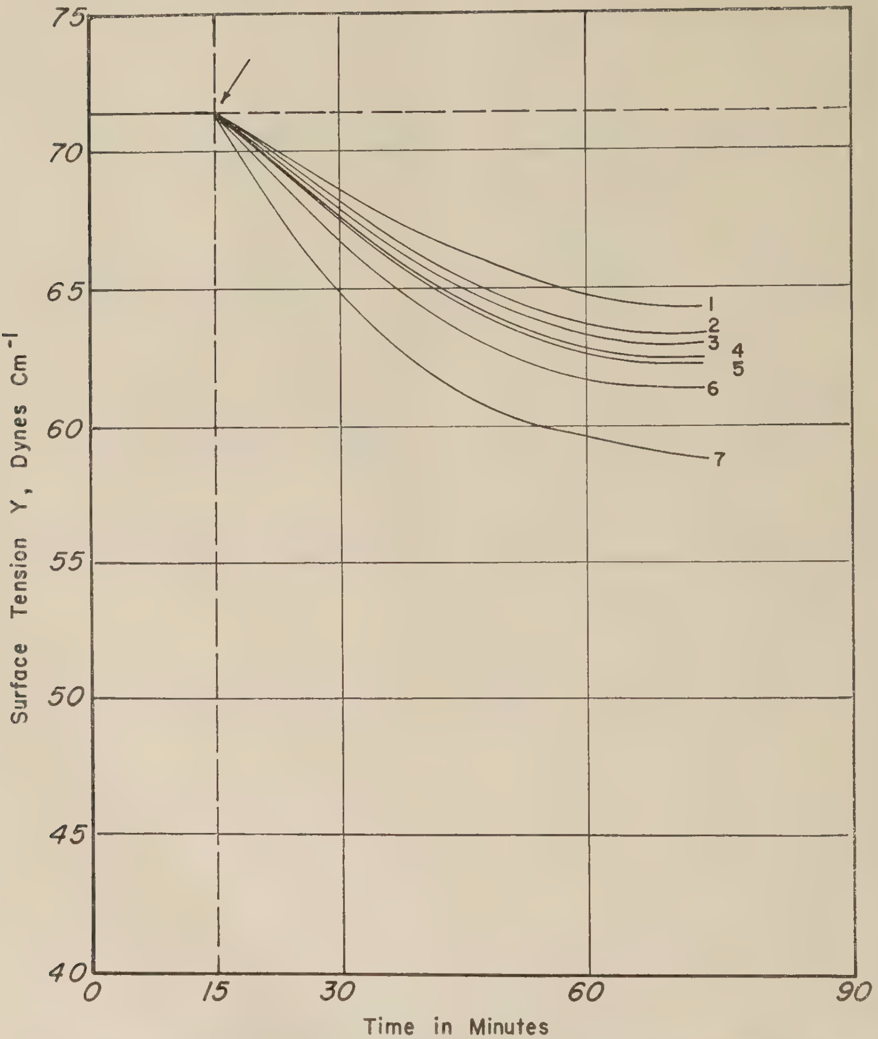

FIGURE 9. Effect of chlorophylls on allyl sulphide solution. Distilled water drop. 1–6. Several different commercial chlorophyll samples; 7. Allyl sulphide solution alone.

The effect of several contaminants on different surface-tension-sensitive liquids is shown in FIGURES 2 and 3. From these two curves, it is evident that different contaminants produce different relative changes in surface tension, depending upon the particular surface-tension sensitive liquid used in the experiment.

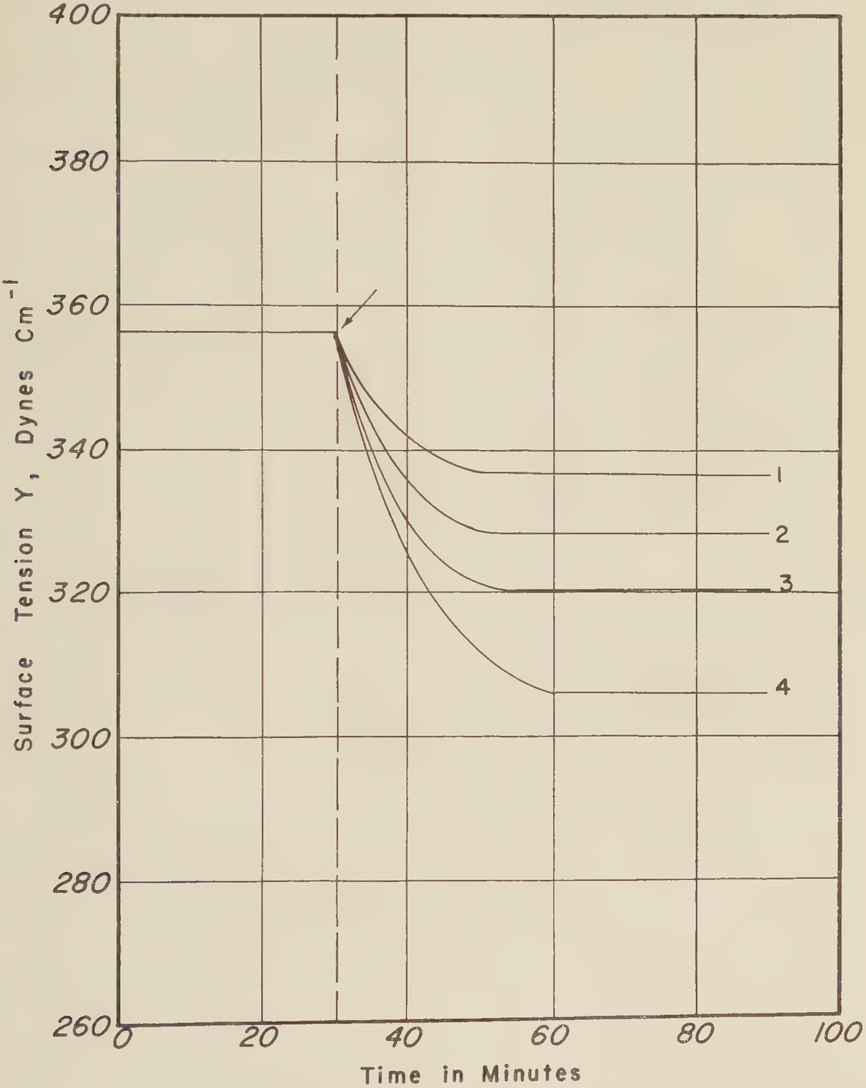

FIGURE 10. Effect of chlorophylls on eugenol. Mercury drop. 1-3. Several different commercial chlorophyll samples; 4. Eugenol solution alone.

When using mercury as a surface-tension-sensitive liquid, certain of its characteristics must be taken into account. The surface tension of uncontaminated mercury is about 460 dynes per centimeter, but drops on exposure of the mercury in moist air to about 350 dynes per centimeter where it becomes stable. In order to use a mercury surface for studying surface tension change, a small container of distilled water was placed in the chamber with the exposed mercury drop. Under this circumstance, the surface tension of the mercury became stabilized before contamination was introduced into the chamber. A mercury surface treated in this fashion is termed "water-stabilized mercury."

The reliability of the surface-tension method of measuring air contamination was studied by making five separate tests of the effect of eugenol on the surface of distilled water. In each, the surface tension was measured at 10 minute intervals over a period of 60 minutes. The results are shown by the curves of FIGURE 4. It may be observed that the surface tension dropped from a value of 71.6 dynes per centimeter (average) to 48.6 dynes per centimeter (average). At no point in the series did the measured value deviate more than 2.0 dynes per centimeter from the mean value for that time interval. The highest standard deviation for any time interval was 0.50 dynes per centimeter. From this series of measurements, it may be concluded that the test method is quite reliable.

The surface-tension method of measurement of air contamination has been applied to the study of the effectiveness of certain deodorants.[2,3] The test procedure has been to obtain surface tension *versus* time curves with a specific amount of standardized solution of an odorous material introduced into the test chamber. The same test was then repeated, but a deodorizing agent was added to the odorous solution and agitated by a shaker for a specified period before introduction into the test chamber. In cases where this method has been used, measurements have shown that the deodorizing material itself did not bring about changes in the surface tension of the test liquid.

The results of tests showing the effect of deodorants on eugenol are presented in FIGURES 5 and 6. From these curves it may be noted that the several deodorant materials tested were quite different in their effectiveness when applied to eliminating the effect of eugenol. The effect of time of contact of the deodorant with the odorant is clearly demonstrated. It is of interest that odor was detectable organoleptically in those tests when surface tension change was noted, and was not detectable when no surface tension change was observed. The effect of certain chlorophylls on eugenol, cineole, and allyl sulphide is shown in FIGURES 7, 8, and 9, all indication being in terms of the surface-tension change of an exposed drop of distilled water. Similar curves measured in terms of the effect on water-stabilized mercury are shown in FIGURE 10.

The work on odor measurement currently in progress at Purdue University may be divided into two sections:

(1) The pendant drop method of surface tension measurement is being used in an extensive study of deodorants. Attention is being given to associating each of several deodorants with the particular odorous materials

on which they are most effective. The number of surface-tension-sensitive liquids suitable for measurements appears to be relatively small. The search for additional liquids is being continued. The technique of measuring the dimensions of the liquid drop is being improved with the objective of reducing the time requirements.

(2) A search is being made for a suitable transducer to convert changes in surface phenomena to changes in an electric circuit. Changes in surface potential are being measured. However, the changes caused by intentional air contamination are usually masked by changes resulting from moisture present in the air.

Research in the two sections is making slow but steady progress. It is planned to report the results of these investigations when significant results are attained.

Summary

(1) A method of measuring the intensity of certain known air contaminants has been described. This method is based on the surface tension change of a liquid drop.

(2) The surface-tension method of measuring air contamination is shown to possess good reliability.

(3) The effectiveness of different deodorants on several specific odorous materials has been shown. The results agree with observations made organoleptically.

(4) Research in this field is continuing in two areas:

(a) The study of the effectiveness of deodorants on certain odorous substances using the surface-tension method;

(b) The search for a method of measuring surface changes by electrical methods.

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OLFACTORY NERVE POTENTIALS A DIRECT MEASURE OF CHEMORECEPTION IN INSECTS*

By Chester Roys
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Various approaches to the study of olfaction have been discussed in this monograph. However, the study of nerve responses to chemical stimulation currently seems to offer the most hope for success in determining the mechanism of this least known of the senses. It may be applied to any animal, but difficulties in reaching the very short and well-protected olfactory nerves of vertebrates have so far prevented direct studies of the chemoreceptors of the nose. Nerve impulses from the chemoreceptors of the vertebrate tongue have been successfully studied in the frog by Pumphrey and in the cat by Pfaffmann. The lack of additional studies on this very interesting material, however, suggests that here, too, there are discouraging technical difficulties. Insects offer important structural advantages over vertebrates for the application of this method to all types of chemoreceptors. A majority of the olfactory receptors are located on the antennae in most insects, and several orders have taste receptors on the tarsi. In either case the receptors are on external surfaces and are joined to the central nervous system by relatively long nerves which are easily located in the appendages (antennae, palpi, or legs) because they form a substantial proportion of the tissue there.

For these structural reasons the general method for electrically recording the nerve impulse is very direct and simple, although the precise technique involves numerous difficulties. Electrical recording of nerve impulses is dependent on the fact that each impulse is accompanied by a measurable electrical change. Most of this work involves changes of the order of 100 microvolts. As the nerve impulse travels along the nerve, that portion of the nerve surface carrying the impulse becomes negative to the normal resting surface. After the impulse has passed, this area recovers to the state of the normal resting surface. Hence, an electrode in contact with the area of the impulse is negative to an electrode on a resting section of nerve and a current flows through the recording device until the impulse passes the electrode. These changes are usually viewed on an oscilloscope and FIGURE 1 shows diagrammatically the pattern produced on the oscilloscope when the nerve is at rest, when the impulse passes the first electrode, and when the impulse passes the second electrode.

Technical difficulties occur principally in the placement of the electrodes. The electrodes themselves are hot-drawn tungsten points soldered to copper leads. The appendage under study is cut off, the electrodes and appendage mounted in wax, and the electrodes inserted in any one of several ways.

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* The work described in this paper was done under contract between the Medical Division, Chemical Corps, U.S. Army, and Tufts College. Under terms of this contract the Chemical Corps neither restricts nor is responsible for the opinions or conclusions of the author.

One of the most successful arrangements is to place one electrode in the cut end of the appendage and insert the other at a joint (FIGURE 2). In general, it may be said that the success of the technique varies directly with the size of the insect, the sharpness of the electrode points, and the experience of the operator. Leads from the electrodes go to an amplifier and thence to an oscilloscope where the trace may be photographed or otherwise recorded. We have found it extremely helpful to record all experiments on a tape recorder, from which they may be played back into the oscilloscope for re-examination or photographing, or permanently stored as tape.

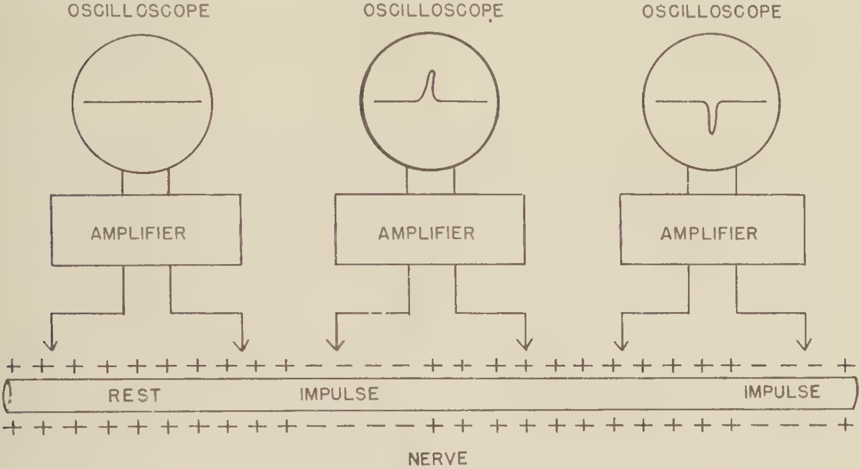

FIGURE 1. Diagram showing pick-up of the electrical change in a nerve during passage of an impulse and its translation into a typical oscilloscope pattern.

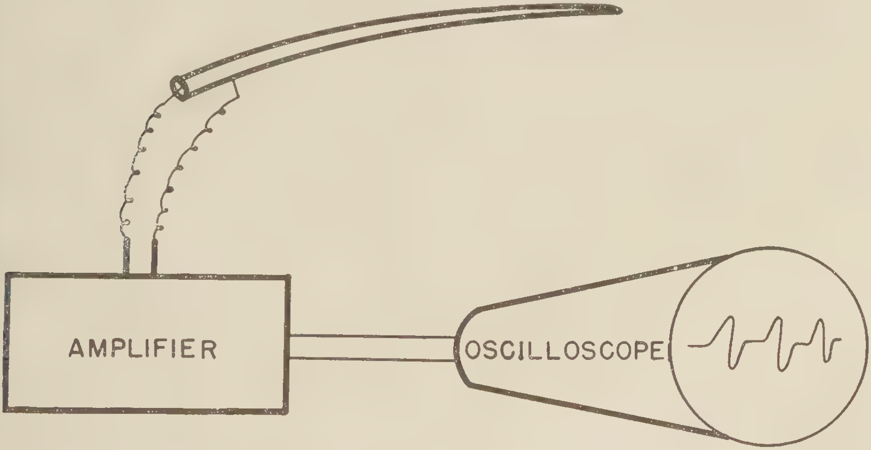

FIGURE 2. Placement of the electrodes in an antenna of the American cockroach. The oscilloscope face shows the passage of three impulses.

With this introduction we may now turn to an examination of experimental results obtained by this method. The first results were obtained in a study of the olfactory thresholds of the American cockroach, *Periplaneta americana*. Responses from antennae and palpi were viewed on the oscilloscope and recorded on an ink-writing device, the Offner crystograph. The potential changes produced by chemical stimulation were much slower than typical nerve potentials (nerve spikes) and appeared to be summations of faster impulses that could not be picked up with the technique used. A typical record is shown in FIGURE 3. It will be noted that the deflections

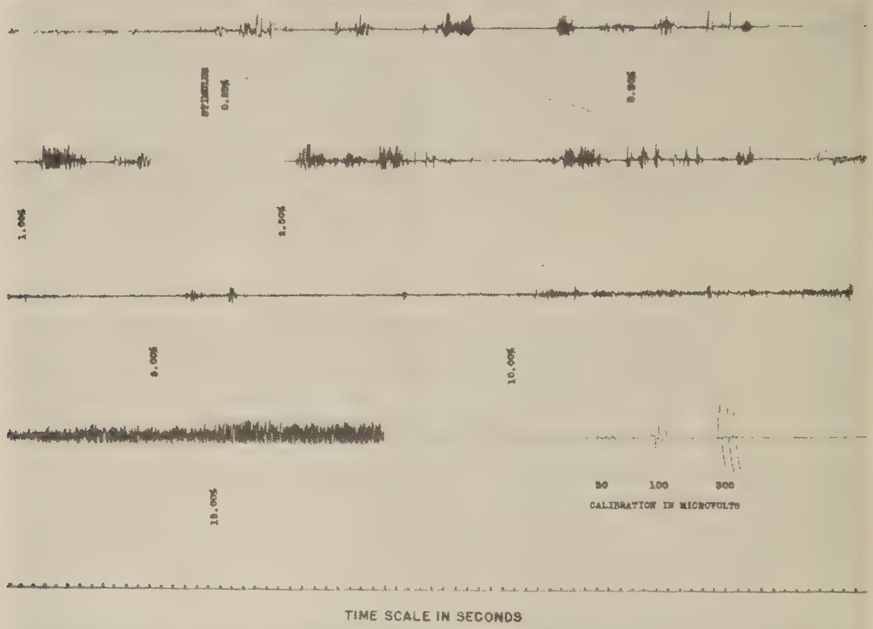

FIGURE 3. Record of the response of a cockroach antenna to stimulation by oil of clove. The notations show the increasing proportion of odorous to odorless air. Record covers 250 seconds.

increase in frequency rather erratically at first, in a way comparable to that in which we smell an evanescent odor near threshold concentration. As the stimulation is increased, they merge into a continuous discharge. In addition to the oil of clove used in the illustration, 19 other odors were selected from the Crocker-Henderson odor classification set to include representative fragrant, acid, burnt, and caprylic qualities. The threshold values obtained for these were in line with those obtained by other workers using behavioral responses (Dethier).

It was apparent from these results, however, that either we were failing to pick up single nerve impulses or we were dealing with a different sort of response in olfactory reception. If it were the former, then improvement in technique was indicated; if the latter, then it should be confirmed as a new phenomenon. On further investigation with improved technique it was found that, when the vapors of benzene, toluene, xylene, and a number of straight chain organic compounds were applied to the cockroach antennae, they produced a pattern of typical nerve spikes as shown in B and C in FIGURE 4. Moreover, these records also show a type of response which seems typical of chemoreception. For, with increasing stimulation (*i.e.*, increasing concentration of the stimulating chemical), the response builds up evenly with more and more spikes per second and then produces bursts of violent activity interspersed with periods of little or no activity (D in FIGURE 4). Line E is a record of the same burst shown in D but recorded by the method used in FIGURES 3 and 5 showing the slow over-all potential change. As stimulation is further increased these bursts become more and more frequent. A record of the bursts, recorded in the same way as the threshold record of FIGURE 3 is shown in FIGURE 5. The similarity between the two records suggests very strongly that in the original threshold records we were recording bursts of spikes too low in amplitude to show as individual spikes (*i.e.*, only the bursts produced sufficient electrical disturbance to be recorded). Another interesting and perhaps very important point about these bursts of nerve activity is their correlation with repellence, at least in the cases of benzene and toluene. In an experiment demonstrating this, several normal cockroaches were confined in a chamber through which was circulated air carrying increasing concentrations of benzene vapor. At low concentrations of benzene they showed either indifference or mild attraction to the incoming mixture, but at exactly the concentration which produced bursts in the antennal nerve preparation, the

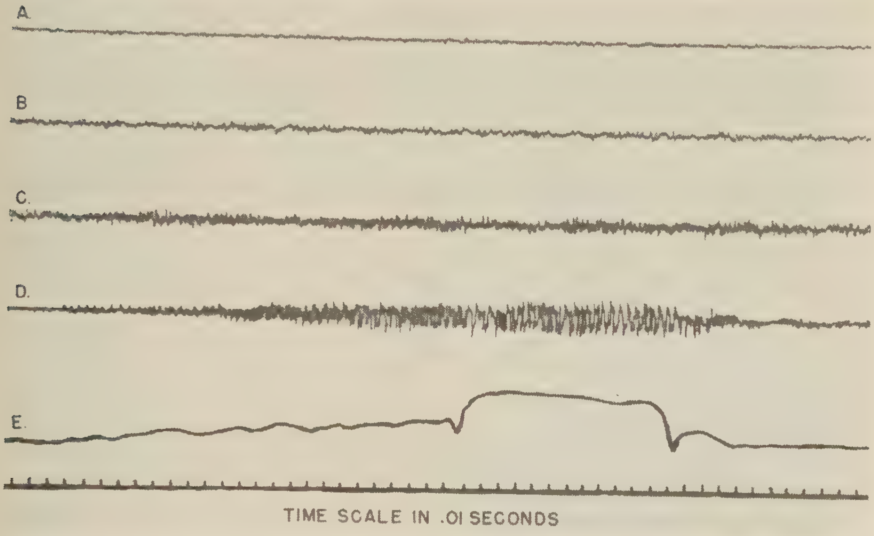

FIGURE 4. Record of the response of a cockroach antenna to stimulation by benzene. A. Baseline before stimulation. B. Initial response to stimulation. C. Response to stronger stimulation. D. Burst of activity in response to still stronger stimulation. E. Record of burst made with writing device which shows only the slow over-all potential change.

cockroaches made violent efforts to avoid the incoming benezene and, if confined in concentrations higher than this, showed muscle spasms, convulsions, and finally death.

Further work has shown that many of the same compounds (notably benzene) also stimulate the legs and other appendages of the insect to produce bursts of spikes. Many insects have taste receptors on the legs and feet, but existing evidence is against the presence of olfactory receptors in these areas. Thus, we are not dealing strictly with olfaction here, but with a common chemical sense which acts through all types of chemoreceptors. Furthermore, even an isolated cockroach nerve cord (corresponding to the spinal cord of vertebrates) responds in the same way to the vapors of these same chemicals. It would appear, therefore, that, in these cases, we are dealing with chemoreception in its most fundamental form, the action of a chemical on an isolated nerve cell to initiate a nerve impulse.

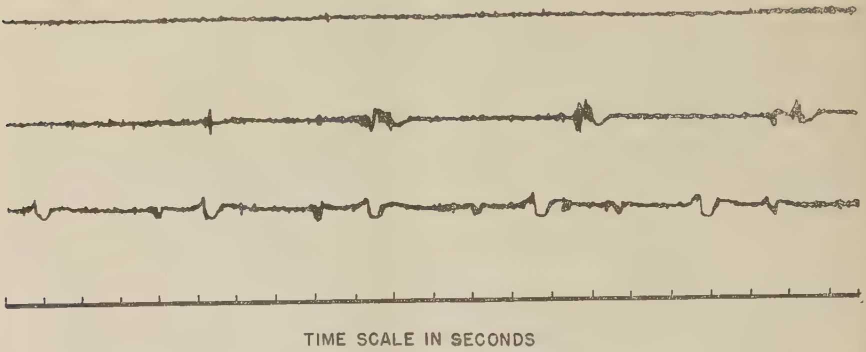

FIGURE 5. Record of response of cockroach antenna to toluene made in the same way as E of FIGURE 4, but covering a period of 66 seconds.

If chemoreception of this sort is a fundamental property of nerve tissue, then it means that no special receptor is needed to translate chemical action into nerve impulses. Moreover, these chemicals produce a quantitative response in the nerve proportional to the amount of stimulation, but there is no qualitative difference apparent in their effect. Therefore, if the insect is to distinguish one chemical of this class from another, it must have special receptors which filter out the effect of some of these chemicals and not others. It is quite easy to imagine a set of receptors, each of which would be more selective to the passage of such chemicals than the next. The least selective would allow all the chemicals to pass and would be a common chemical receptor, the most selective would allow only a few, perhaps only one chemical to pass and would be the most highly specialized receptor. At present there is no experimental evidence for this theory of filtering, nor is there sufficient evidence to state whether these responses should be classed as common chemical sense, olfaction, taste, or a combination of any two or all three of these. Furthermore, we are dealing only with the effect of a limited class of odorous chemicals and our results may or may not have wider application to other types of chemoreception. This approach, however, does offer a working method, and a working hypothesis for further investigation, and a better understanding of the nervous response to airborne chemical vapors—and, by most definitions of the term, this may be considered as a better understanding of olfaction.

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THE OSMATIC RESPONSES OF NORMAL AND NEUROTIC MONKEYS*

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It is our purpose in this paper to report a special study of the role of olfaction in normal and in experimentally induced neurotic behavior in monkeys for possible comparison with similar patterns in human conduct.

Procedures

Subjects. Our group of 18 monkeys consisted of ten Asian Rhesus, two African Vervets, one African Sooty Mangabey and five American Spiders, ranging in age from about 1½ years through full maturity.

Observations and training. The individual traits of each animal, its relationships with cage-mates and with other members of the colony and its reactions to a wide variety of situations were observed and recorded for from four to 24 months. Specific training was simultaneously conducted in a special apparatus† with facilities for the presentation by remote control of stimuli in all modalities, fixed and mobile switches by which the animals could manipulate various signals, food boxes into which fruit was automatically delivered, and a ventilation system designed to present single or combined odors for periods as short as 3 seconds. The animals learned to master the following skills: (1) to open one of two food boxes on a differential visual or auditory signal; (2) to manipulate one of two electric switches from 1 to 4 times as a means of actuating the proper feeding signal; and (3) to choose the correct one of these switches in response to specific cues.

Specific olfactory reactions. These were studied by allowing the animals spontaneous access to open containers of odorant materials, by putting odorous substances directly on their food, by injecting odors singly or in combination into the experimental apparatus, and by association of odors to feeding or other meaningful experiences.

Induction of neuroses. After the control period of observation and training, each monkey was subjected to a series of motivational conflicts between its learned feeding responses and its aversion to a toy rubber snake projected at unexpected intervals into the food box. After from 12 to 15 such "psychologically traumatic" experiences, the monkeys developed experimental neuroses variously characterized by hypersensitivity to all stimuli; frequent and often violent startle and phobic reactions; inhibitions of feeding, play, and exploratory activities; severe neuromuscular and organic dysfunctions; markedly increased auto- and homo-erotism; hallucinatory and delusional patterns; and persistent alterations in social rela-

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* This study was supported by a special grant from Airkem, Inc., New York.

† This apparatus was illustrated and described in greater detail in previous reports.[1, 2]

tionships parallel to those that occur in human neuroses and psychoses. These symptoms and their exacerbation or relief by various experimental procedures have been described in detail elsewhere;[1,2,3] in the present report, we are concerned primarily with the olfactory aspects of the neurotic behavior.

Olfactory Behavior

Spontaneous avidity. Normal monkeys were usually attracted to open dishes containing fluids with a fruity odor—orange, lemon, strawberry, cherry, pineapple—or scents such as bay oil or vanilla. The animals approached these frequently and occasionally drank a small quantity of the solutions. Anise, root beer, or pine needle oil were less attractive; and other odors were given but scant attention. However, no odor tested, including musk, skunk oil, valerian, indol, and onion or garlic concentrates, was definitely avoided.

Odors as cues. Measured intensities of odors, in contrast to visual or auditory stimuli, proved to be relatively ineffective as signals for manipulating switches and securing food, nor could established audio-visual responses be readily transferred to the olfactory modality. This relative indifference to olfactory influences on conditioned feeding behavior was in dramatic contrast to the acuity and significance of olfactory discriminations shown by the same monkeys (see below) when they were subsequently made neurotic.

Neurotic behavior in relation to olfaction. During the period in which the animals were being subjected to the neurotigenic motivational conflicts, they were repeatedly exposed to olfactory stimuli not directly associated with either hunger or fear; *i.e.*, random injections of butter flavoring or lily-of-the-valley at three minute intervals, or a constant atmosphere of dilute bay-oil aerosol within the apparatus for from one-half to one hour, or vanillin placed directly on food rewards not accompanied by the appearance of the toy snake. None of these stimuli significantly modified the spontaneous or learned behavior of the animals; *i.e.*, these scents remained devoid of operational meaning.

When, however, oil of anise was put on fruit offered coincidentally with the appearance of the snake, or oil of lemon or pine needles was injected into the apparatus at this juncture, the monkeys showed marked changes in subsequent reactions to these olfactory experiences. Thus after three to five such associations the monkeys not only rejected previously welcomed tidbits smelling of anise, lemon, or pine needles—sometimes throwing them away violently—but refused all food and showed severe anxiety, phobic and escape reactions to the injections of these scents into the experimental cage even when they were combined with one or more other odors. When escape was impossible, the monkeys would cower in a corner of the apparatus peering at the food box and around them in all directions, respond to minor sensory stimuli with intense startle and urination or defecation and often refuse all food in the laboratory for the entire day—behavior closely similar to that elicited by the original exposure to the snake itself. Further, as the neurosis grew more severe, reactions to olfactory stimuli became generalized so that previously neutral odors such as bergamot or ylang ylang produced apprehension, hyperactivity, and temporary suspension of food-taking. Moreover, these reactions occurred not only in the experimental apparatus but with almost equal severity anywhere in the laboratory and in lesser degree in the animals' living quarters.

Adverse associative responses. As part of the experimental design, three animals were permitted to have normally satisfying associations to the aroma of lemon during the period of preliminary observation and training and were then made neurotic without relating this odor directly to their conflictful experiences. In subsequent unsuccessful attempts to alleviate their neuroses by various drugs, these monkeys were given milk containing either alcohol, mephenesin, or sodium pentathol. After experiencing the effects of these drugs on three occasions, the animals refused to take them again, apparently relating the odor (imperceptible to humans in the case of the solutions of mephenesin or pentathol) with other neurotic aversions. When lemon oil was added to the drug solutions, the animals refused not only this new mixture but all liquids smelling of lemon, even after 72 hours of deprivation of their usual fluids. In effect, although the scent of lemon represented only a tertiary generalization (conflict to drug to lemon) of their conflictful experience, the animals sometimes reacted to its exhibition as violently as though it heralded the appearance of the snake itself.

Olfactory behavior during recovery from neuroses. After from eight to 12 months of observation in the neurotic state, our animals were treated for an additional five to 11 months by various methods designed to re-establish relatively normal conduct;[1,3] in this interval special studies were also made of the corresponding changes in their olfactory behavior. It was found that the recovery of the animals could be set back for as long as six weeks if they were exposed too early in the process of re-training to odors such as anise or pine needles which had been rendered traumatic by direct association with their former conflicts, or to lemon which had been only indirectly related to the traumatic experiences. Phobic responses to these odors persisted for about three months after the monkeys had virtually ceased aversive reactions to noises, lights, or previously disturbing stimuli in other modalities.

Olfactory categories. Our observations indicated that the re-acceptance of odors followed definite perceptive groupings: thus, where lemon was traumatic, lime, orange, and strawberry were also avoided in decreasing order of intensity. Similarly, when pine needle oil was phobogenic, balsam, eucalyptus, and cedarwood were correspondingly avoided, although in lesser degree. As recovery from neurosis proceeded, previously neutral odors were first re-accepted; then those related to anise, lemon, or pine needles; and finally the triad of odors which had been directly associated with the neurotigenic conflict (FIGURE 1). However, these three odors were never again perceived with complete equanimity; instead the animals remained overly sensitive to all olfactory experiences and were likely to be suspicious of places with unaccustomed odors and to refuse strangely scented food without attempting to taste it. In this connection it may be noted that the three monkeys treated with alcohol and other drugs continued for a number of months to reject all food or fluid contaminated with these even when the amounts were sufficiently slight to be imperceptible to human taste or smell.

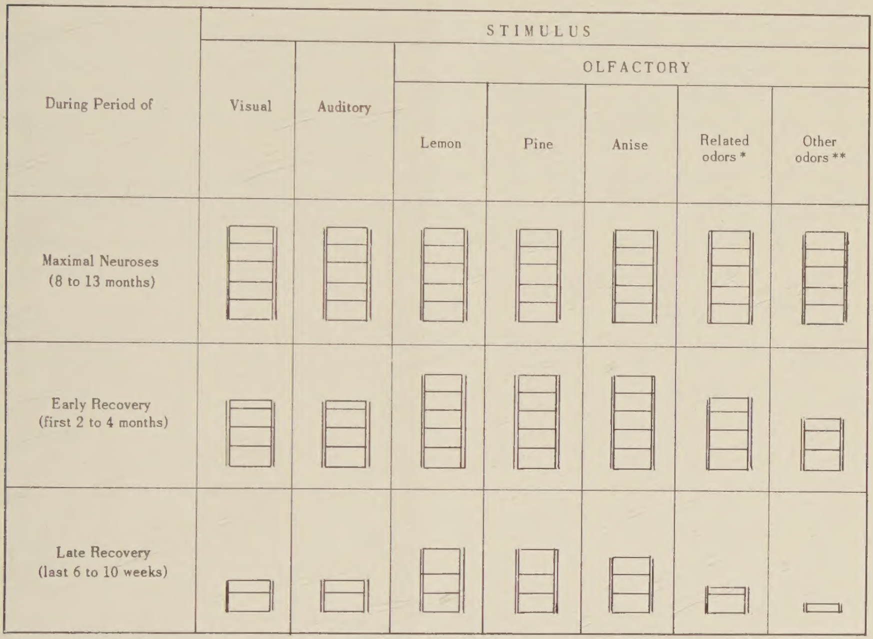

FIGURE 1. The scaled degree of aversive reaction by monkeys to stimuli in different modalities for different times in the recovery period. The figures in the cells of the table represent the mean score for all monkeys. The score for each monkey was the mean of five separate ratings. The basis for the various ratings was as follows: 0. No change in the reaction of the animal in response to the stimulus. 1. Slowing of current activity (feeding, *etc.*); increased alertness. 2. Cessation of current activity, with restlessness of a transient nature. 3. Pacing, occasional urination, defecation, and apprehensive examination of surroundings; reaction continuing 5 to 10 minutes after exposure. 4. Increasing response, characterized by stronger autonomic reactions (defecation, horripilation, *etc.*) and some accentuation of the neurotic symptomatology of the particular animal; responses continuing from 10 to 30 minutes after exposure to the stimulus. 5. Maximum response, characterized by hyperactivity, strong autonomic reactions, extreme exacerbation of the neurotic symptomatology of the particular animal, and occasional panic; continuing from 30 to 60 minutes after exposure.

* Related odors refers to lime, orange, and strawberry in relation to lemon, and to cedarwood, balsam, and eucalyptus in relation to pine needles. In most cases the figures represent ratings from nine animals as each of the experimental animals was not presented with every odor.

** These odors included artificial butter flavoring, lily-of-the-valley, bay oil, vanillin, and skunk oil.

Action of deodorants. During the course of the experiments, we tested various types of deodorant compounds, either as exposed directly in the apparatus or when blown into it in measured quantities along with various odors being studied. One of these deodorants, a commercial chlorophyll compound, prevented the phobic reactions of the sensitized monkeys to the disturbing odors such as lemon and pine needles; indeed, even when this compound was added to the air stream soon enough after the adverse responses to a traumatic odor had started, the latter were quickly and sometimes dramatically relieved. Studies are being continued with various forms of this product to determine the mode of action of its ingredients.

Motion pictures have been taken of the apparatus, methods, and some of the experiments here described, and are available for distribution.

Summary

The olfactory behavior of eighteen monkeys was studied with regard to (a) spontaneous preferences, (b) the effects of odors on learned feeding responses, (c) the association of odors under various conditions with induced motivational conflicts and their resultant neurotic manifestations, and (d) the action of deodorants on these olfactory patterns. Our conclusions are:

(1) An odor becomes relatively attractive to an animal when it is spontaneously related to biodynamic satisfactions such as normal feeding, or is experimentally associated with such experiences. Conversely, an odor becomes unacceptable when it is associated with unpleasant or motivationally conflictual situations.

(2) In the latter case, olfactory phobias can become sufficiently severe to impair seriously the general adaptive capacities of the monkey and hinder its return to normal patterns of conduct.

(3) Aversive reactions to a specific odor tend to generalize to related odors and to become more intense and persistent than parallel reactions in other sensory modalities.

(4) As neurotic aversions are mitigated by various forms of therapy, odors are once again tolerated according to special groupings, but re-acceptance of odors directly associated with traumatic experiences is never complete.

(5) Phobic reactions to specific odors can be prevented or markedly diminished by a chlorophyll-containing deodorant; however, the mode of action of this compound was not determined.

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